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Volume XXI Toronto, November, 1943 Number 2

The University of Toronto Medical Journal

(AN UNDERGRADUATE PUBLICATION)

This journal is published six times a year, November to April, by the Medical Society of the University of Toronto, to serve as a medium for student expression and to bring to the student recent articles of scientific interest.

$1.50 per volume. 25c. per single copy.

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EDITORIAL

HEALTH INSURANCE

SECTION II*

Plan—Outline of the Projected Act

(a) Organization
  (i) Dominion
  (ii) Provincial
(b) Sources of Revenue
(c) Methods of Obtaining Revenue

(a) *Organization*

In accordance with the recommendations of the Rowell-Sirois Report on Dominion-Provincial Affairs, it is proposed to place the bulk of management of Public Health and Hospitals in the hands of the Provinces and for this purpose the Advisory Committee on Health Insurance has drafted the "Model Act" which in generalities will be outlined below. The only responsibility of the Dominion Government is to pass the "Enabling Act."

The Dominion Bill therefore is concerned with (a) assistance of the Province in the effectual application of the Health Insurance Act by giving grants in aid; (b) placing at their disposal information, statistics and experts to be used in the

*This is a continuation of a series of articles inaugurated in the October JOURNAL.

solving of their particular problems; (c) the establishment of a National Council on Health Insurance advisory to the Minister of Pensions and National Health and finally (d) the provision of grants to be administered by the provinces aimed at National Health problems, including tuberculosis, venereal disease, professional training of doctors, engineers and nurses, investigational programs, physical fitness and a final all-inclusive grant termed the "General Public Health Grant" which includes preventive medicine, education, mental hygiene, child and maternal hygiene and some 20 other medico-social problems. Grants in aid are contingent upon the provinces living up to the requirements of the "Model Act" or an Act with substantially the same provisions.

The Provincial Bill is concerned with the making effective those procedures which entitle the Province to the grants in aid made by the Dominion, and secondly the establishment of facilities for the medical, surgical, obstetrical, dental, pharmaceutical, nursing, and hospital services for the ensured in the province. These duties are to be carried out by the Provincial Health Insurance Commission, which has certain prescribed functions defined by the terms of the Act.

(b) *Sources of Revenue*

All disbursements will be made from the Consolidated Revenue Fund of the province. This will be re-imbursed by (1) Contributions of the insured, and (2) Grants from the Dominion Government.

The approximate computed expenditure for all Canada (assuming the cost of medical services to be $232,896,000—as it was in 1938—and the cost of administration of the scheme to be 10% of the total cost) is $256,186,000. This sum is to be divided between self-supporting direct contributions from the ensured individuals and the public treasury in the proportion of 48.7% by the benefactors and 51.3% by the general revenue fund.

(c) *Methods of Obtaining Revenues*

Dominion contributions will come if the Province complies with the requirements of the "Model Act."

It is planned to collect the revenue from the individual contributors by payroll deductions and the sale of Health Insurance Stamps and Books somewhat in the manner Unemployment Insurance administration is carried out.

For purposes of the Act the general population is divided into two groups, (a) "employed contributors" who derive their income from payments from an employer, and (b) "assessed contributors" who derive their income from capital invested or from sources other than wages.

Employed contributors are to pay a certain fixed percentage of the wages received without exceeding a certain fixed sum. An example may make this clear.

Assume the cost of medical services per annum in Canada to be $240,500,000 as it was in 1935, and, using the 1939 population figures, it can be calculated that the cost of medical services divided equally amongst all persons 16 years of age or over, amounts to $26.45 per capita. For the sake of calculation this can be accepted as $26.00 or 50 cents a week per capita.

Therefore the fixed sum which is not to be exceeded is $26. The fixed percentage has been tentatively set at 3%. Thus for an individual with no dependants the critical income is $866. Below this level the man pays 3%

of his total wage and the difference between this and $26 is paid by his employer. Above this level he pays $26 regardless of what percentage it is of his income.

Secondly, consider the case of a man with an income between $866 and $1400 who has one dependant. This man, on the fixed sum basis, is liable to pay $52 (i.e. $26 for himself and $26 for his dependant). On the other hand, this exceeds 3% of his income. Such an individual is required to pay a minimum of 0.7% of his income toward the dependant's share. Now suppose the man earns $1000 and has one dependant:

For himself he contributes.....$26.00
For his dependant he contributes.....$ 7.00 (0.7% × 1000)
3% of his income is.....$30.00

The Act requires that under such circumstances the man shall contribute his full 3% plus 0.7% for his dependant. This amounts to $37 per annum. The difference between this and the total deficit of $52 is made up by the Province and amounts to $15 per annum.

Children under 16 years of age are not considered dependants under this Act. The object of this exclusion is the relatively great medical cost involved in having and raising a family. Sir William Beveridge expresses the view that such economic considerations are undoubtedly a factor in the low birth rate in England and for this he recommends out and out benefits for raising families. This plan effectively avoids awarding cash benefits for raising a family.

Assessed contributors are persons having an income from real or personal property. The Act provides that such property shall be assessed by the parcel method and an equalized value is obtained which is representative of the valuation placed upon the property both by the municipality and the Health Insurance Commission. Between 3% and 3½% is the levy to be placed on such property with the fixed sum of $26 per annum per capita as the maximum payment required.

The remaining situation which has not been mentioned with regard to revenues is the decision as to the portion of the total expenditure which is to be borne by the Province and the portion by the Dominion. Various figures have been proposed. The Minister of Pensions and National Health in a Report on Social Security stated that in the event that the Rowell-Sirois Report is accepted or in the event that wartime revenue measures are continued after the war, the Dominion share of the cost will probably exceed 1/6 of the total expenditure or will amount to at least $3.60 per person per annum.

The revenues will therefore be raised along the lines of the following scheme:

	Amount	Percentage	
Employees	$ 63,542,000	24.8%	
Employers	24,172,000	9.4%	
Assessed Contributor	37,036,000	14.5%	
			48.7%
Treasury	131,436,000	51.3%	
			51.3%
	$256,186,000		100.0%

Of this $131,436,000 which is supposed to come from the treasury, approximately $15,000,000 can be subtracted for grants now given to hospitals which

will not be required after the advent of Health Insurance. Therefore $116,436,000 must be supplied from the public treasury. Now, if the Dominion accepts the responsibility for 1/6 of the total expenditure, this will amount to $40,352,000 paid by the Dominion and the remaining $76,084,000 will be split among the nine provinces in proportion to their populations. It has also been suggested that this scheme be further supplemented by the Dominion accepting the responsibility for 1/3 of the provincial deficits.

This increasing function of the Dominion Government in the administration of the general revenue fund of the entire country constitutes one of the objections raised by some parties to the Rowell-Sirois Report, for it has occurred to the provincial prime ministers that revenue formerly spent in their own provinces is now being taken away from the wealthy provinces to be spent in those less well-to-do.

In the foregoing an attempt has been made to show how vast and intricate the financing of such a social security scheme can be. There are many aspects to which no reference has been made and many more which have not yet been worked out. However, if any reader desires further information concerning any aspect of the above, an effort will be made to enlighten him if he will mail his question or questions to Room 107 in the Anatomy Building.

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THE HISTIDINE PREGNANCY TEST

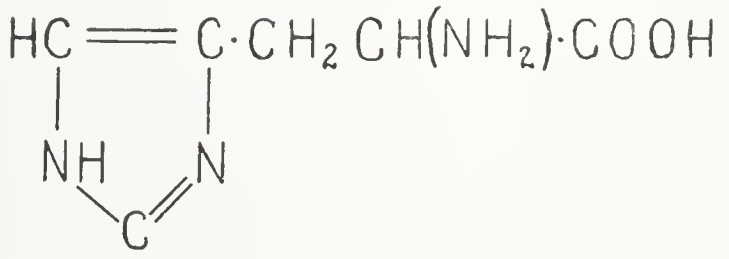
A. H. JAMES, B.A. (Oxon) 4T4

From the Dept. of Biochemistry, St. Michael's Hospital

The popularity of biological tests for pregnancy depends upon their high degree of accuracy: aside from this, they have many disadvantages, requiring a stock of animals and taking some time for their performance; a pregnancy test may sometimes be required in a surgical emergency. Interest in chemical tests for pregnancy has been stimulated by the current shortage of experimental animals; one of the foremost of these tests is that based on the constant presence of amino acid histidine in pregnancy urine.

In 1908, Knoop (1), in the course of some researches on the constitution of histidine, noticed and reported a colour reaction produced by bromination of that acid. The quantitative absorption of bromine was used as a method of estimating histidine by Plimmer and Phillipps (2). In 1929, Voge (3) reported very briefly some results of pregnancy tests using Knoop's colour reaction, and found that they corresponded very closely with Ascheim-Zondek tests. The first intensive studies on histidinuria in pregnancy were made by Kapeller-Adler (4), starting in 1933. She found that histidine appeared in the urine very soon after conception, and that it was continually present throughout pregnancy in amounts varying from 15 to 50 mgm. per 100 c.c. This metabolic curiosity is peculiar to man, and is said to depend on the inhibition during pregnancy of a specific ferment histidinase, present in the liver, due to the action of which histidine is normally broken down before it is excreted. Histidinuria occurring in non-pregnant women is transient, rarely lasting more than a day.

In bare outline, the test is performed in the following way. To the solution to be tested, bromine water is added until an excess of bromine exists, as demonstrated by starch iodide paper. The excess is then allowed to wear off, and when it has completely disappeared, an ammonia buffer is added, and the solution placed in a boiling water bath: a purple colour develops if histidine is present, later changing to brown with the formation of a deposit of amorphous black flakes. The chemical mechanism of the reaction is, to a large extent, unknown. Histidine has the constitution:



being β imidazole-α amino-propionic acid.

According to Plimmer and Philipps, each molecule of histidine takes up two atoms of bromine, and although the dibromo-derivative has not been isolated by anology with the diiodo-derivatives it would appear that the bromine saturates the carbon-carbon double bond in the imidazole ring. The further changes responsible for the formation of the purple colour are largely a matter of speculation: Kapeller-Adler states that complex rings are built up, and that the alanine portion of the molecule forms a part of them.

Reagents

Bromine Reagent

Bromine	5 c.c.
Glacial Acetic Acid	500 c.c.
Water	1000 c.c.

Ammonia Buffer

.880 Ammonia	400 c.c.
10% Ammonium Carbonate	200 c.c.

5 c.c. of urine are placed in a test tube, and the bromine reagent added as described below. When the excess has worn off, 0.5 c.c. of the ammonia buffer are added, and the tube placed in a boiling water bath. The test should be performed on acid or neutral urine: alkaline urine contains nitrites which interfere with the reaction: a method is described of oxidizing alkaline urines with permanganate before bromination, but this has not proved very satisfactory.

Bromine is a reactive element, and must enter into chemical combination with many of the constituents of urine, of which histidine is an occasional one. The quantity of bromine reagent required to produce an excess of bromine in different specimens must therefore be expected to vary greatly. A large excess of the reagent cannot be added, since persistent excess of bromine interferes with the reaction.

I attempted to determine the manner of disappearance of bromine by an experiment such as the following: to 5 c.c. of urine, different quantities of bromine reagent were added and the time during which an excess persisted in each case was measured. For one sample, up to 2 c.c. caused an excess which disappeared almost instantaneously. After the addition of 2.0-3.5 c.c., bromine was detectable for proportionately increasing lengths of time, 6 minutes in the case of 3.5 c.c. Greater amounts than this disappeared very slowly indeed. The conclusion to be drawn would appear to be that bromine disappears from urine (a) by a rapid reaction, (b) by a slow reaction, and (c) by diffusion. For the successful detection of histidine, an appreciable amount of the slow reaction must be allowed to occur. Many of our early failures to detect histidine were due to the addition of insufficient bromine. Rule 1 for bromination, (see below), is based on these findings.

The sure method of detecting the presence of excess bromine is the use of starch iodide paper. But colour changes are observed during the addition of bromine to an aqueous solution of histidine. An amber colour is first developed, which, as more bromine is added, is gradually blended; a deepening yellow is finally produced, due to excess of bromine. In many cases, these changes can be followed in urine, but often, the initial colouration is absent, so that one may be deceived into adding an overwhelming excess of bromine. With practice it is possible to distinguish the amber colouration from a simple excess of bromine.

If bromination has been successfully carried out, the resulting solution should be pale yellow in colour. There should be no hint of brown; if this latter cannot be removed by the addition of more bromine, the test should be repeated.

With regard to practical details, the bromination should be carried out in a good light, and in such a manner that the solution can be observed against a white background. If this is done, it will be found that the consumption of starch iodide paper can be considerably reduced. The quantity of bromine reagent added should be noted, for a reason to be mentioned below, and the addition is therefore most conveniently made from a burette. Bromine water is an unpleasant reagent, and attacks the lubricant used in the burette so that the latter is apt to leak. This might make the test inconvenient for most office practices.

The quantity of bromine added ranges roughly from 1.0 to 5.0 c.c., and is not related to the presence or absence of histidine, nor to the intensity of the colour

reaction if it is present. The average amount for 25 positives was 2.35 c.c., ranging from 1.2 to 5.0, and for 16 negatives, 2.14, varying from 1.2 to 3.6. Most of the bromine must react with substances other than histidine.

Every now and again, a urine will be encountered which reacts with an inordinate amount of bromine, with or without the formation of a precipitate. Two examples may be of interest.

Two specimens sent up for histidine tests required 8-10 c.c. of bromine, addition of which produced a fairly heavy white precipitate. If sufficient bromine was added, however, an excess could be produced which satisfied the criteria. Inquiry revealed that both these patients were receiving sulphathiazole, and it was possible to get the washed precipitate, into solution at an acid pH, and diazotize it; coupling with N-1-naphthyl-ethylenediamine then produced the characteristic colour given with sulphonamides. Other cases have been encountered since then, and although we have not had the opportunity to examine the urine of a pregnant patient receiving sulphonamide, I see no reason to suppose that the reaction would be interfered with, provided sufficient bromine is added.

In another case, nearly 20 c.c. of bromine reacted instantly with the urine, an end point being reached suddenly, once past which, no excess could be made to disappear. The substance responsible for this has not been identified.

In summary, the three following rules are the criteria of successful bromination:

(1) An excess of bromine must persist in the solution for not less than one minute.
(2) The excess must disappear completely within 5 minutes.
(3) The resulting solution must be of a pale yellow colour.

To the brominated solution are added, without delay, 0.5 c.c. of the ammonia buffer, and the solution at once mixed thoroughly. pH_4 is said to be the desirable reaction, and I tried the effect of bringing the solution accurately to this pH instead of adding a routine amount of buffer, but the colour was in no way enhanced, and 0.5 c.c. of buffer seems satisfactory in all cases.

The tube is now placed in a boiling water bath; a beaker is most satisfactory since the solution must be watched from the first: there should be a white background.

In a not inconsiderable number of cases, the vivid purple colour observed by Knoop, with ultimate deposition of black flakes, leaves no doubt as to the presence of histidine. But in a greater number, the reaction is less marked, and care and experience are necessary to distinguish a true positive from the troublesome colours which sometimes appear in negative urines. Three characteristics of the positive reaction serve to distinguish it in most cases.

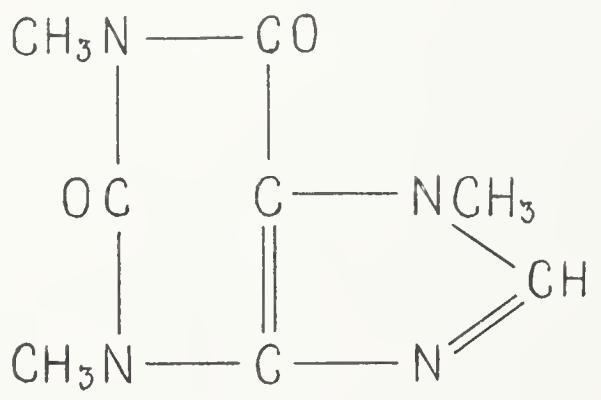
(1) The colour commences within a few seconds of placing the tube in the water bath.
(2) It commences near the surface of the solution, spreading downwards.
(3) The colour is purple or occasionally reddish, but never brown.

The chief source of confusion is the fact that all positive reactions change to brown sooner or later, and the weaker the reaction, the more readily does it turn brown, so that the purple colour may be fleeting. Further, a large number of non-pregnant urines turn brown, and I cannot help feeling that the many reports of false positives are due to mistaking this change for a true positive. A brown colour in the solution after a minute or more is of

no significance whatever; the three rules must be considered in each case regardless of the depth of the final colour.

Considerable thought has been given to the nature of the substance responsible for the brown colour in negative urines: if it could be identified, it might be possible to eliminate it from the diet, if that were the source, or to remove it chemically if it were of metabolic origin. It might be of interest to mention an example of a suspicious substance which was tested.

Caffeine has the constitution:



and it will be seen that part of its molecule bears some resemblance to the imidazole ring of histidine. To a specimen of non-pregnant urine which did not give a brown colour to any marked degree, some caffeine was added, and a histidine test carried out. A brown, almost red, colour appeared rapidly, and the final colour was quite a deep brown. An experiment was hastily organized in which four female subjects abstained from tea, coffee and Coca-Cola for 24 hours, and provided specimens before and after a meal which included tea and coffee in fairly large amounts. The results were disappointing. The post prandial specimens were dilute, and gave little brown colour, whereas those in which caffeine was supposedly absent, developed, with one exception, a fairly deep brown. Investigations continue.

In general, any colour developing in a non-pregnant urine does so fairly slowly, and uniformly throughout the solution. Occasional cases have been noted of a reddish brown spreading fairly rapidly from the top: most of these have been in post partum patients.

No known substance has been encountered which interferes with the reaction: it does not appear to be necessary to filter cloudy urines as most of them are cleared by the acid in the bromine reagent.

Before presenting results, the important group of cases must be mentioned which makes it necessary to note the volume of bromine reagent added. This is that group which requires less than 1.2 c.c. of reagent to produce satisfactory bromination. In such cases, the majority of those containing histidine will fail to give the colour reaction. They either remain pale yellow or become faintly pink: the non-pregnant specimens remain pale. In no case has a pregnant urine requiring 1.2 c.c. or more failed to give a positive reaction, and for this reason, 1.2 c.c. is chosen as the deadline. In two or three cases I have been able to demonstrate histidine in urines requiring less than this, in one case as little as 0.6 c.c., but these are exceptional. Unless a fairly marked colour is produced, judgment should be reserved on any case requiring less than 1.2 c.c. The reason for the failure of the colour to appear is simply that the urine is too dilute. A more concentrated specimen should therefore be awaited. The only advantage of morning specimens in routine hospital practice is that they are almost always sufficiently concentrated.

Reports as to the accuracy of the test are confusing, especially with regard to false positives. Neuweiler and Grimm (5) report an accuracy of 99.3 per cent. Following the potassium permanganate modification (which she has since rejected), Kapeller-Adler obtained 96 per cent positives. Wong (personal communication) had three errors in 250 cases. It appears,

therefore, that in some hands, the test can be made to compare with the Friedman as far as accuracy is concerned. With regard to false positives, some workers report as many as 25 per cent. Goodfriend and Daniel (6) found 5 in 72 non-pregnant cases. I must have examined nearly one hundred non-pregnant urines and have only come across two false positives, one patient having varicose veins and the other fibroids. Negative tests were obtained in both cases a short while afterwards.

I have records of tests on fifty-three patients, pregnant, non-pregnant and post partum. Of 26 pregnant patients, 5 specimens were too dilute to be reported; (the specimens were taken from out-patients clinic held in the early afternoon). This left 21, of which 20 were reported positive and one negative. The negative urine was a brownish colour after bromination and therefore suspect. 13 non-pregnant specimens were all reported negative; these were taken from patients with a variety of complaints, gynaecological and otherwise. I have since done many more non-pregnant specimens, and, as noted above, found two transient false positives.

There were 14 post partum specimens tested in this series. There is great variability in the time taken for histidine to disappear from the urine: doing tests every four hours after birth, I have watched it disappear in 16 hours: on the other hand, I have obtained a positive result in a 21 day post partum patient in hospital for pyelitis. On the average, the test becomes negative in three or four days.

The known pregnant cases in this series were attending prenatal clinic, and none were less than three months pregnant. Wong states that she has had plenty of positive reactions in women who have missed one period, and come to clinic at once. It is not an easy matter to find patients less than two months pregnant. One case is under observation at the present time who has had a positive histidine for two and a half months, with enlargement of the uterus, but who has continued menstruating and has had two negative Friedman tests.

We have had, unfortunately, a notable lack of success in the three cases where a pregnancy test was required prior to surgery. Such failures are difficult to eradicate from one's memory. It is to be hoped, however, that improvements in technique will be forthcoming. If the above mentioned mechanism of the production of histidinuria is correct, it should be possible to carry out something in the nature of a histidine tolerance test, or at any rate, to increase the amount of histidine in the urine by providing a diet rich in the acid. It may also be possible to improve the test from the chemical viewpoint. It would be worth a good deal of investigation to place in the hands of the physician a rapid test for pregnancy which he can perform for himself.

My thanks are due to Mr. M. O. O'Sullivan, M.A., of this department, Dr. P. J. Moloney and Dr. E. W. McHenry, for valuable assistance and suggestions, and to Miss Anne Pape for assistance with the manuscript.

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FATAL RESULTS OF SULPHONAMIDES*

B. BERRIS, B.A., 4T4 AND G. L. SNIDER, 4T4

Considering the wide use of sulphonamides for a long and varied list of conditions, the number of fatal cases due to the drug is relatively small. However, toxic reactions which have not ended in fatalities, but which are nevertheless serious, are common. These toxic reactions can affect practically any system in the body.

The main systems affected are:

1. The urinary system.
2. The hemopoietic.
3. The skin.
4. The cardiovascular system.
5. The liver.
6. The nervous system.

Each system will be discussed where possible under the headings:

1. Manifestations of the toxic reactions.
2. Pathological lesions.
3. The mechanisms involved.

Details of treatment will not be mentioned, but certain general principles will be discussed wherever applicable.

The Urinary System

Fatal complications in the urinary tract are more common than elsewhere in the body. Sulphanilamide rarely causes such complications. The responsible drugs are sulphapyridine, sulphathiazole and sulphadiazine.

The clinical signs and symptoms referrable to the urinary system vary. The minimal sign of renal damage may be microscopic haematuria which may clear up or give marked haematuria. Severe renal or ureteral pain may be the first manifestation. The patient may exhibit sudden anuria, but more often there is first oliguria which, if unrecognized, may proceed to anuria. When this occurs, there is a rise in non-protein nitrogen, and then the frank signs of uremia may appear. Crystals may occur in the urine with no untoward effects. (1)

Pathologically, the gross picture is not characteristic. The kidneys are oedematous; often show petechial haemorrhages, and the glistening of crystals on the cut surface. The pelves and ureters may be normal, but more often there are submucosal haemorrhages, petechial or somewhat larger. The renal pelves and ureters are occasionally filled with crystals, blood, fibrin, and amorphous substance which may extend into the papillary ducts. Frequently crystals are seen encrusted about and impacted in the ureteral orifices. Concretions varying in size can occur in the kidney, pelvis, ureter or bladder. Ulceration adjacent to calculi is not uncommon. In a few cases calculi have been large enough to cause obstruction, with a resultant hydronephrosis.

The most outstanding microscopic change in the kidney is the presence of areas of focal coagulation necrosis, which occurs also in many other organs in the body. There is often an infiltration in and around these areas, of eosinophiles, mononuclears and less commonly of polymorphs. There is no surrounding zone of hyperemia. This, coupled with the fact that the kidney is sterile on culture, strongly suggests that these lesions are not bacterial in origin. In some cases similar cellular infiltration is seen in the stroma, independent of areas of focal necrosis.

**This paper was presented before Alpha Omega Alpha Society on May 17, 1943, at the home of Dr. R. R. Graham.*

The glomeruli show a tendency to increased cellularity, and pink hyaline material and an occasional red blood cell in Bowman's capsule. In some cases, certain of the convoluted tubules show a nephrotic change with dilatation of the tubules, swelling and disintegration of the cytoplasm, and pyknosis and disappearance of the nuclei. The tubules may be filled with cellular debris, granular casts, red blood cells and crystals. Basophilic oval or round concretions are occasionally seen.

At the Banting Institute, we studied the microscopic sections of six cases that had received sulphonamide therapy, and which showed kidney lesions. In only two of these cases was death attributable to the drug. The only lesion observed outside the kidneys was a myocardial infiltration in one case. Definite focal necrosis was seen in only one case—one of those which died because of the drug. It was difficult to be sure of a nephrotic change, because of post-mortem degeneration, but there was no doubt about it in at least three of the six cases. In two of the cases, small basophilic discoid bodies were seen in the tubules. These concretions have been shown to be a combination of the sulphonamide with calcium; the crystals of the pure sulphonamide dissolve out in the paraffin embedded section (8). The most constant glomerular change that we observed was pink hyaline exudate in Bowman's space. In only one case was blood seen in Bowman's space, and in the tubules (7).

The mechanisms of production of haematuria, calculi and anuria will now be discussed.

1. *Haematuria*

The cause of the haematuria is by no means clear. There are two possible mechanisms: (a) a primary toxic affect and (b) haematuria secondary to trauma.

The primary toxic affect is independent of crystalluria. The evidence for this is is that red blood cells can be seen in Bowman's capsule whereas crystallization occurs in the tubular system.

Haematuria secondary to trauma is dependent on crystal formation. The evidence for this is that areas of necrosis have been seen in the tubules adjacent to crystals; because of the sharp edged nature of these crystals, it has been suggested that these damage the capillaries adjacent to the tubule and thus give rise to haematuria. Indirect experimental evidence to this effect has recently been offered. It has been found that feeding animals urea together with the sulphonamide prevents their precipitation in the kidneys. Since crystallization occurs in the tubules the inflammatory lesions in the glomeruli as manifested by increased cellularity of the tuft and thickening of Bowman's capsule seems hard to explain if the toxic theory is denied entirely. Although experimentally such glomerular lesions can be produced by ligation of the ureter (8). This has not been proven for man and we believe that both mechanisms are at work.

2. *The mechanism of calculus formation*

Several factors influence the deposition of the concretions (9). These are:

(1) The concentration of the drug in the urine.
(2) The degree of acetylation of the drug.
(3) Urinary stasis.
(4) The pH of the urine.
(5) The temperature of the urine.
(6) The drug used.

Each of these factors will be discussed in turn.

(1) *The concentration of the drug in the urine.*

This depends on the amount of drug in the blood stream, the volume of fluid

passing through the kidneys and the renal function. It can be controlled clinically by varying the dose of the drug, and the fluid intake of the patient. Therefore, both the dose of the drug and the fluid intake will have a pronounced effect on calculus formation.

(2) *The degree of acetylation.*

The crystals in the kidney have been found to be composed mainly of the acetylated form of the sulphonamides, whereas there is very little of the free form. With the exception of sulphadiazine, the acetylated form is much more insoluble than the free form, and, therefore, the degree of acetylation influences the deposition of the drug. Experimentally, glucuronic acid and mixtures of animo acetic acid, choline, cystine, calcium glucuronate and ascorbic acid have been used to prevent the conjugation of the sulfa drugs, without interfering with their therapeutic value. In these experiments the incidence of calculus formation is greatly decreased (10) (11). It is important to determine whether such medication is equally effective in human beings.

(3) *Urinary stasis*

It has been found that when urine is allowed to stand with the temperature maintained, sulphonamide crystals settle out of the urine, suggesting that stasis is important in the production of the crystals. This is borne out by the observation that crystals are more abundant in the bladder than elsewhere in the urinary tract. In addition, calculi are often observed proximal to an obstruction (3). Practically, little consideration is taken of this factor when the drug is being administered.

(4) *pH*

In the determination of the solubility of sulphathiazole, sulphadiazine, and sulphapyridine and their acetyl derivatives in normal human urine, a marked increase in the solubility of sulphathiazole, and sulphadiazine and their acetyl derivatives occurs quite suddenly as the pH goes from 7 to 8, that is, within the normal pH range of urine, but with sulphapyridine, as the pH goes from 9 to 10, which is beyond the normal pH range of urine. This sudden change in solubility is due to the fact that these drugs and their acetyl derivatives are weak acids which ionize and form soluble salts in an alkaline medium,

In applying these results in dogs, it was found that acidifying the urine by ammonium chloride administration caused a sulphadiazine or sulphathiazole crystalluria; alkaliniation of the urine by sodium bicarbonate administration prevented this crystalluria from occurring. It has been noted that in nearly all instances of renal calculus formation, the urine was acid. In experiments on two cases of subacute bacterial endocarditis, massive doses of sulphadiazine were administered, and the urine maintained alkaline with large doses of bicarbonate. High concentrations of the drug were thus held in the urine without crystalluria occurring. Hence it would appear that making the urine alkaline to litmus is effective in preventing calculus formation with sulphathiazole and sulphadiazine, but not with sulphapyridine.

(5) *Temperature*

It is common laboratory experience that as urine cools, sulphonamides are precipitated. Experiments in vitro have shown that the solubility of the sulphonamides increases as the temperature increases. This may serve to explain why, when crystalluria and anuria result in febrile patients with high concentrations of sulphonamides in the urine, they occur shortly after the temperature drops. This

has little practical application in preventing or treating urinary complications.

(6) *The drug used*

Renal complications are rare with sulphanilamide compounds, commoner with sulphathiazole, sulphadiazine and sulphapyridine. This difference is due to the relatively greater solubility of sulphanilamide and its acetylated products in the urine.

Summing up, the factors governing calculus formation which can be controlled clinically are: the drug used, the dose of the drug, the fluid intake and the pH of the urine; the other factors are as yet of academic interest only.

Suppression of Urine

This can occur in three possible ways:

1. Due to a nephrotic change in the tubules (26).

2. Due to mechanical obstruction by crystals either in the tubules, pelves, or ureters.

3. Due to obstruction of the tubules with haemoglobin following hemolytic anemia.

With sulphapyridine the concretions tend to be in the pelves and ureters and lavage is of great value in overcoming the anuria. On the other hand, sulphathiazole tends to be precipitated in the tubules. For this reason lavage is less important; fortunately, the anuria frequently clears up after the drug is stopped (13). In a review of sixteen cases of sulphadiazine anuria during the past year, mechanical obstruction in the ureters occurred in eleven cases, and all but one were relieved by ureteral catheterization and lavage. The other five cases terminating in death showed an acute calcifying nephrosis. These cases were not relieved by ureteral catheterization.

In hemolytic anemia, the accepted cause of the anuria is blockage of the tubules with hemoglobin. However, the question has been raised by one group of workers as to whether the anuria is due to this or to the shock which accompanies the anemia (14). Blockage of tubules by hemoglobin is probably the more important of the two.

The treatment of urinary tract complications will now be discussed briefly.

The most important principle in the treatment is prophylaxis, and early recognition of the complications when they do occur. Prophylaxis consists mainly of discriminating and controlled use of the drug together with a maintenance of the fluid intake. Although definite confirmation is still lacking, experimental evidence suggests that maintaining an alkaline urine during the administration of the drug is worthwhile. Because of the relationship of solubility to temperature, it might be a good idea to force fluids when the temperature drops in febrile patients receiving these drugs.

The earliest manifestations of urinary tract complications may be oliguria,haematuria or renal or ureteral pain. Opinions differ as to whether microscopic haematuria is an indication for stopping the drug, but on the appearance of gross haematuria, renal or ureteral pain, severe oliguria or anuria, the drug should be stopped at once. With moderate haematuria or oligura, in cases where it is considered that sulphonamide therapy is essential, a less toxic drug like sulphadiazine may be substituted. Fluids should be forced to maintain the urine at 1000 c.c. or more. In the presenece of extreme oliguria or anuria, renal or ureteral pain, ureteral catheterization and lavage with a warm alkaline solution should be carried out.

The Haematopoietic System

The blood dyscrasias which may be produced by the sulphonamide drugs include

granulocytopaenia, hemolytic anaemia, leukemoid reaction, thrombocytopaenic purpura and aplastic anaemia. The leukomoid reaction and the aplastic anaemia have not been fatal, but will be mentioned for the sake of completeness. The mechanism of production of blood dyscrasias will be discussed at the end of the section.

Acute Hemolytic Anaemia

Sulphonamide therapy is frequently accompanied by a varying degree of hemolytic anaemia. The anaemia begins on the second or third day of therapy, progresses, and is likely to be seen with increasing severity as treatment is prolonged. This is the so-called chronic hemolytic anaemia.

Occasionally an acute type of hemolytic anaemia characterized by a precipitous drop in hemoglobin and red blood cells is seen. This type of anaemia is of sudden onset and may reach dangerous levels within twenty-four hours. Clinically the patient may display jaundice, pallor, nausea, vomiting, fever, hepatomegally and splenomegally. Examination of the blood reveals reticulocytosis, increase in serum bilirubin, and at times marked leukocytosis. The increase in white blood count may at times reach levels in the vicinity of one hundred thousand per cu. m.m.—the so-called leukemoid reaction. Rarely, this may occur apart from hemolytic anaemia, but no deleterious effect has been noted when therapy was continued in such patients. Haemoglobinuria may be present. This anaemia is more likely to follow drug therapy with sulphanilamide or sulphapyridine, although it has been reported with sulphathiazole therapy. In acute hemolytic anaemia there is a high incidence of mortality—6 out of 9 cases in one series (14).

The pathological changes are not characteristic, resembling those seen in hemolytic anaemia due to other causes. The skin is icteric. The spleen is enlarged, due to engorgement with blood. The liver is oedematous. Microscopically, the phagocytic cells in both organs are enlarged, and show an abundance of iron-containing pigment and fragmented erythrocytes. Small foci of four or five necrotic liver cells have been reported (14); the author suggested that they might have been caused by occlusion of capillaries due to Kupffer cell proliferation.

The principles of treatment are: immediate cessation of chemotherapy, repeated transfusion, and the alkalinization of the urine if haemoglobinuria is apparent.

Aplastic Anaemia

Only one case of aplastic anaemia has been reported. This occurred after the administration of sulphathiazole and cleared up after cessation of therapy and transfusion. Sternal puncture at the height of the dyscrasia showed marked hypoplasia involving all cellular elements (15).

Leukopaenia, Granulopaenia, and Agranulocytosis

Depression of the number of white blood cells occurs much less frequently following sulphonamide therapy than reduction in the number of red blood cells. Generally, the granulocytes are most affected when depression does occur. The most serious complication is malignant neutropaenia terminating in fatal agranulocytosis. This appears most commonly two to three weeks after starting administration of the drug, and is most frequent in those who have received a large amount of the drug continuously for that length of time. Agranulocytosis may occur after the cessation of chemotherapy.

Clinically, the onset of agranulocytosis is accompanied by fever, sore throat,

ulcerative stomatitis, pharyngitis, and a skin eruption. Death occurs from the infection for which the patient is being treated or from intercurrent infection (16) (17).

Pathologically, it is found that in infectious lesions in these cases, polymorphonuclear leucocytes are conspicuous by their absence — for example, in a pneumonia the infiltration is not extensive and consists largely of monocytes. The bone marrow is characterized by a lack of maturation of the granulocytic series of the white cells.

The treatment consists mainly of prophylaxis, because once agranulocytosis has developed, it is fatal in a very high percentage of cases. Prophylaxis includes frequent routine white blood cells count in all patients receiving chemotherapy, and cessation of drug treatment if the count falls below 3500-4000 per cu. m.m. The white count should be followed for one week after cessation of chemotherapy, especially if the course has been long. Where possible, a course of drug therapy should not exceed two weeks (1).

Thrombocytopaenic Purpura (18)

Thrombocytopaenic purpura haemorrhagica is extremely rare, eight cases having been reported to date. These have followed the use of sulphanilamide, sulphapyridine, sulphathiazole and sulphadiazine. The mortality has been fifty per cent.

Clinically, the disease is characterized by purpuric eruptions in the skin, face and extremities, epistaxis, bleeding from the gums, scleral haemorrhage, vaginal bleeding, hematuria and blood in the stool. Examination of the blood reveals no abnormality, other than greatly diminished platelets. It is important from the standpoint of prophylaxis that thrombocytopaenia occurs before haemorrhage.

At post mortem, multiple haemorrhages are found; the bone marrow is normal.

In the treatment, early recognition of the disease followed by cessation of therapy is important if the patient is to recover. It has thus been suggested that the number of platelets should be noted in the smear when the blood is being checked for possible granulocytopaenia during sulphonamide therapy. Transfusion has been used to treat the disease, but its value is doubtful.

The Mechanism of Production of Blood Dyscrasias

No definite statement can be made as to the pathogenesis of the blood dyscrasias, but it appears that the fundamental mechanism is the same as that for the benzene and aniline compounds. The evidence for this is, firstly, that there is similarity in chemical structure of the drugs; secondly, the clinical and pathological manifestations of toxic reactions following their administration is the same, as far as the hemopoietic system is concerned, and finally, there is both direct and indirect evidence that a small amount of the drug is metabolized in the body to give oxidation products analogous to those of benzene and aniline. It has been suggested that these oxidation products may account for the toxic effects on the hemopoietic system (18).

The mechanism of hemolytic anaemia is not clear. The sulphonamides like benzene and aniline have a direct effect on the cells of the peripheral circulation. Within the first few hours after the onset of anaemia there is a striking but transitory increase in the fragility of the erythrocytes. In vitro, while a saturated solution of these drugs in normal saline will not produce hemolysis of red blood cells, they accelerate the rate at which hemolysis occurs in the presence of a known lysin.

This property may account for the production of the hemolytic anaemia encountered during the administration of sulphonamides (18). Evidence has recently been offered that hemoglobinuria *per se* is not the cause of death. There is rapid destruction of erythrocytes with decrease in blood volume. This may be responsible in part for the production of the clinical picture of shock, which not infrequently is associated with anuria (14).

The Skin

If we eliminate the nausea and vomiting caused by sulphapyridine, the skin eruptions are the commonest toxic manifestations following sulphonamide administration. These are commonest with sulphathiazole, least common with sulphadiazine. The eruptions due to the sulphonamides are characterized by their pleomorphism. The types of lesions have been described as erythematous, morbilliform, maculopapular, erythema multiforme, vesicular; bullous, urticarial, exfoliative and purpuric. A nodular eruption sometimes associated with sulphathiazole administration has been described. This has not been encountered previously in any other disease or condition (19).

The number of fatal cases which can be definitely attributed to a skin lesion is small, and most of these would appear to be due to exfoliative dermatitis. This condition is characterized by a widespread shedding of the skin leaving a brilliant red, raw, beefy surface.

Skin eruptions usually appear after the drug has been given for five to seven days. They may occur earlier or much later. They may be accompanied by other toxic reactions such as fever, chills and nausea and vomiting. Splenomegally it is not uncommon—generalized adenopathy has been observed (1).

The pathogenesis of the skin eruptions differs in individual cases. One type of lesion appears to be associated with sulphanilamide and photosensitivity, occurring only on the surfaces of the body that have been exposed to sunlight or ultraviolet light. Photosensitivity in patients taking other sulphonamides has not been observed (20) (21). Another group of lesions may be termed toxic dermatoses. These may subside even when drug therapy is continued, and do not reoccur on administration of the drug at a later period. A third group of lesions appears to be the result of a true drug sensitivity. As therapy is continued, signs of toxicity become more manifest. The patient may experience a marked eruption when the compound is administered in a small dose after an interval of weeks or months. The tissue reaction may have been induced by one drug, but any one of the compounds given at a future time may incite a skin reaction (1).

The principles of treatment are cessation of administration of the drug and substitution therapy if it is absolutely essential to continue treatment with sulphonamides.

The Cardiovascular System

Clinically cardiovascular involvement is not common. Two types of lesions have been described: one in the blood vessels, the other in the myocardium.

The Blood Vessels

Two cases of periarteritis nodosa have been reported (22) (23). In one case of carcinoma of the scrotum receiving sulphonamides, the lesions of periarteritis nodosa were not present in the tissues of the scrotum removed five months and one week before the toxic reaction occurred, but were present there and widespread throughout the body at post mortem, nine days after the reaction.

The lesions described are necrosis and hyalinization of the affected arteries together with infiltration, perivascularly, or of the entire wall by mononuclear and polymorphonuclear leucocytes. Eosinophiles were present in some vessels, haemorrhage about the lesions in others. Widespread focal necrosis similar to that already described was noted. The necroses in these cases appears to develop as a result of damage to minute capillaries and arterioles—the focal inflammatory infiltrations developed immediately about a necrotic minute vessel. This is the only suggestion that has been offered as to the etiology of focal necrosis.

The Myocardium

The characteristic lesion in the heart takes the form of an interstitial myocarditis. In the histological examination of 283 patients who received sulphonamides, 44% showed this lesion.

The myocardial lesion consisted of an interstitial cellular infiltration, chiefly perivascular, but also occurring more diffusely in the severer cases. The myocardium was widely involved in both auricles and ventricles; the looser auricular myocardium was often more densely infiltrated than the more compact ventricular muscle. The infiltration included large mononuclears and eosinophiles. Parenchymatous degeneration was noted in the form of slight Zenkers necrosis but no simple or liquifaction necrosis was seen.

Since this series was described in the early months of 1942 numerous other authors have reported similar myocardial changes. They have been seen alone, in conjunction with widespread focal necrosis, and with periarteritis nodosa.

We have observed two cases, similar, though not identical to those of the original series; in neither of these was death attributable to the sulphonamide though one of them showed a sulphonamide nephrosis.

The evidence suggests that both these lesions have a common basis in hypersensitivity. No strict correlation between the duration and intensity of medication, and the severity of the myocarditis could be found in the clinical material. This suggests that idiosyncrasy is a factor, especially in view of the eosinophilic character of the infiltrations. Furthermore, both of these lesions occur in the presence of serum sickness in humans, and can be produced in animals by sensitization to foreign proteins.

Two cases of cardiac arrhythmias have been reported following the administration of sulphonamides. In one, the electrocardiogram revealed signs of myocardial degeneration and nodal rhythm. The only cause to which this could be attributed was the administration of the sulphonamides (24) (25).

THE LIVER

Sulphonamides may cause varying degrees of liver damage in human beings. Sulphanilamide is the worst offender, sulphapyridine, sulphathiazole and sulphadiazine are less toxic, and in that order. Although hepatic disfunction tends to be transitory in most patients, fatal liver necrosis may occur. The latter is more likely to appear in patients having previously damaged livers, such as occur in portal or biliary cirrhosis (1).

The signs and symptoms of hepatites are anorexia, epigastric distress, nausea, and at times, vomiting. Pain in the right upper quadrant of the abdomen, enlarged tender liver, jaundice, hyperbilirubinaemia and decreased hepatic function occur, except in mild cases. Jaundice may also occur in acute hemolytic anaemia, but the presence of jaundice must be looked on as evidence of relative liver disfunction.

In fatal cases the picture is one of acute yellow atrophy with a small soft liver, and microscopically, widespread extensive destruction of hepatic cells. Focal necrosis similar to that seen in the kidney has been described (27).

When hepatitis appears, chemotherapy should be discontinued, and a diet high in carbohydrate and protein but low in fat, given. If it is essential that chemotherapy be continued, or if there is evidence of liver impairment in a case about to be treated, sulphathiazole or sulphadiazine should be used cautiously (1).

The Nervous System

The toxic reactions in the nervous system are of two types: Those following systemic administration of sulphonamides and those following local application to the brain.

The toxic reactions following systemic administration of the drugs are diverse. They include nausea and vomiting, diarrhoea, headache, dizziness and tinnitus most commonly; of less frequent occurrence are: dysmorphopsia, aphasia, agraphia, stammering, toxic psychosis, peripheral neuritis, encephelopathy, myelitis, optic neuritis, transitory myopia, meningeal signs, blindness and convulsions. The only fatal cases which have been reported have been due to myeloencephelopathy. Of the two cases we have seen reported in the literature, one showed a typical ascending myelitis (28), the other was clinically an encephalitis.

In addition, deaths have been reported due to the intracranial use of sulphathiazole (29). Ten cases are reported of application of sulphathiazole to the brain in craniatomies. Five of the six frontal explorations were complicated by post operative epilepsy; two of these patients died in status epilepticus. In the remaining frontal operation the dura was not opened and no epilepsy occurred. In the four cases of lateral or posterior craniotomies epilepsy did not occur, not even in one case with a previous history of epilepsy.

In animal experiments no such exclusive localization was observed though the epilepsy was more severe and persistent when the anterior basal region of the cerebrum was chosen for experiment.

Sulphanilamide, sulphapyridine and sulphadiazine can be used freely on the cerebral surface without the risk of epilepsy. Therefore the eleptogenic property of sulphathiazole seems to be associated with the thiazole part of the molecule.

General Consideration of the Pathogenesis of the Toxic Reactions

It could be anticipated that if the sulphonamide compounds interfered with the metabolic activity of bacterial cells, they would interfere with the cellular metabolism of the host.

The pathogenesis of the drug reactions is not clearly understood. It is difficult to differentiate the manifestations on a purely toxic basis or on the basis of temporary and permanent drug hypersensitivity. Some individuals have reactions quite early in the course of treatment, and yet they have no history of having received one of the sulphonamide drugs in the past. It is possible that a few of these patients were sensitized previously by drugs having similar chemical structure, e.g. arsphenamine (1).

A considerable number of patients may take one of the compounds for several days and have no ill effects from the drug, but on a subsequent occasion may manifest reactions when small doses of the same drug are ingested. In one study in which sulphathiazole was given to patients who had not had a febrile reaction on a first course of the drug, 36% developed fever, mostly on the first day (30).

In general the initial reactions caused by a sulphonamide compound occur only after the drug has been taken for several days. However, on a subsequent occasion a violent reaction may be precipitated immediately after a single small dose of the compound is administered. One feature is becoming more apparent—that is, that an increasing number of people are acquiring sulphonamide hypersensitivity (1).

Direct skin tests are of little value in the detection of hypersensitivity. A patient may react violently when the drug is administered per os and not at all when the drug is injected intradermally, but it is found that incidence of the skin reactions is greater when the sulphonamide is first incubated with the patient's serum (31). In experimental animals, hypersensitivity has been produced by the administration of sulphonamide bound to protein; hypersensitivity could not be produced with the sulphonamide or protein alone (32).

Further evidence of the existence of hypersensitivity is that the drug rash resembles serum sickness rash; and that interstitial myocarditis and periarteritis nodosa may both occur in serum sickness without sulphonamide therapy. Eosinophiles so frequently seen in the cellular exudates in the various organs is also suggestive (22).

Conclusion

One thing is clear. There is a definite if small risk attached to sulphonamide administration, and if this risk is to be minimized, certain conditions should be fulfilled:

1. The indications for the use of the drug should be definite.

2. The physician should be acquainted with the risks involved, the early manifestations of toxicity and prophylactic and treatment measures.

* * *

The authors wish to thank Professor Wm. Boyd and Dr. A. Postiloff for their co-operation in providing material for study, and for their aid in interpreting the microscopic sections.

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THE EFFECT OF SULPHONAMIDES ON ACUTE OSTEOMYELITIS

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It must be remembered that the effect of these drugs will depend on the method in which they are used. At the Hospital for Sick Children they recommend doses of 8-10 gms. daily for a child of eight, or better—whatever dose is necessary to maintain a blood level of 6-12 mgm.'s per cent. On the charts that I saw of actual cases in that hospital, doses of 18 grams a day and blood levels of over 20 mgm.'s per cent were recorded.

It is generally accepted that sulphonamides

Do

1. Prevent deaths (by giving heavy doses early). Previous mortality, 22%. Using sulphonamides H.S.C. series of 89 cases with 5 deaths gives a mortality of 5.5%.

2. Rapidly bring about negative blood cultures, i.e., end of pyemia or septicaemia.

3. Secondary lesions are greatly reduced in frequency and those occurring appear to be milder than would be expected.

4. The duration of (a) acute illness, (b) stay in hospital, is reduced.

5. Prevent local complications occurring as frequently.

Do Not

1. Interfere with the antigenic effect of the infection or prevent the formation of antibodies.

2. Prevent the local reaction, i.e., the local part does show the signs of acute inflammation and a local abscess will develop unless the drug has been given very early.

Controversial

The effect of surgical intervention at a later stage after treatment with sulphonamides has not definitely been settled. The proponents of no surgical interference whatsoever claim that sequestration is much less common with their treatment and that the sequestra that do form are small and are dealt with spontaneously as sterile bone grafts. They point out that osteomyelitis is really a septicaemia and what you do locally is not going to help such a general condition. Further, the operation diminishes the local blood supply, allows the seepage of serum containing the drug, and allows secondary infection. They admit that in some of their cases the abscess ruptures spontaneously and these appear to be the cases that do not do so well, develop persistent sinuses and sequestra that must be removed surgically.

The other aspect is that sulphonamides appear to be of little value in the presence of frank pus anywhere, whereas surgical drainage is the accepted and well-proven treatment.

Is osteomyelitis the exception to this sound surgical rule?

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FRACTURES IN GENERAL

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The subject of fractures is an immense one and it is impossible to outline a complete discussion of them in such a short article. In the following account I shall attempt to discuss fractures in general, leaving specific fractures until a later date. It is my desire that some of the difficulties regarding this subject which arise in the minds of those who are in their junior clinical years will be cleared up, at least in part if not entirely.

Definition

There have been many definitions set forth in the past years of the term "fracture" but probably the most straightforward definition is: "a sudden solution of continuity in bone usually resulting from external violence."

Causes

The causes of fractures are widely varied. It is wise to divide the causes first into two main groups, namely: (*a*) Predisposing Causes, and (*b*) Exciting Causes. These are in turn subdivided as follows:

A.—*Predisposing Causes*

1. *Age:* From two to four years of age fractures are not uncommon, owing to the unsteady gait and frequent falls to which little children are liable; from four to six years of age the bones often bend so as to cause green-stick fractures; up until the age of eighteen, at which time most epiphyses have united with their respective diaphyses, epiphyseal separation is common; from six years on, fractures increase in their frequency until their maximum is reached, between thirty and forty years of age; finally, in old people, we find fractures due to the bones becoming atrophic or brittle.

2. *Sex:* Up until the age of four or five, fractures are seen equally distributed between the two sexes; in adolescence and adulthood they are more frequent in males; and finally, over forty-five years of age, they are more frequent in females.

3. *Occupation:* Today, with so many of our population in Active Service and in war industry, we must realize the importance of this predisposing cause, more so than ever before, for training of our men and our speed-up in heavy labour exposes these people to a much greater danger of external violence.

4. *Morbid Conditions of the Bones:* These conditions predispose in a marked manner to what is known as Spontaneous Fracture, in which the determining force cannot be recognized or is very slight. Under this heading are included:

(a) Atrophy of bone.—This may be of the senile type, as manifested especially in the cervix femoris; or due to the want of use as in a paralyzed limb or from an ankylosed joint.

(b) Certain nervous or mental diseases. —Patients afflicted with general paralysis or tabes dorsalis are unduly liable to fracture, which may occur in apparently healthy bones.

(c) Osteogenesis imperfecta — This consists in an inherited tendency to spontaneous fracture.

(d) General bone diseases. — These consist of such diseases as rickets and osteomolocia.

(e) Local bone diseases. — These, in turn, consist of such diseases as sarcoma, secondary carcinoma, acute osteomyelitis, and the erosion of aneurisms.

B.—*Exciting Causes.* These are threefold:—

1. *Direct violence,* such as incurred by a bullet or car. The fracture line is at the site of blow and usually transverse, not infrequently comminuted and sometimes complicated.

2. *Indirect violence.* Here the accident is usually produced by the compression or bending of the bone with such force as to exceed the limits of its natural elasticity, so that it yields at the weakest spot. The usual result is an oblique fracture line and if any torsion is present as by forced inversion or eversion of the foot, a spiral fracture line will occur.

3. *Muscular action.* This is the most common cause in small bones into which powerful muscles are inserted, namely, the patella and olecranon.

Varieties of Fractures

The various types or varieties of fractures are best divided into three main groups, namely,

A.—According to physical conditions at the site.

B.—Fractures of normal bones that require much force to break them.

C.—Fractures of abnormal bones that require little force to break them.

Now, the main group tabulated "A" is further subdivided as follows:

A.—*According to physical conditions at the site.*

(i) *Complete*—

1. *Closed (Simple) Fracture.* This is one in which the skin is unbroken or where the external air has no admission to the site of fracture.

(a) Transverse. The fracture line is straight across the bone. It is due to direct violence and many spicules are not uncommonly found.

(b) Oblique. The fracture line is on an oblique plane to that of the bone. It is usually due to a combination of indirect and direct violence.

(c) Spiral. The fracture line occurs along the line of stress. It is usually due to indirect violence with the element of torsion added.

(d) Longitudinal. The fracture line is in the long axis of the bone. It is frequently seen in gunshot wounds.

2. *Open (Compound) Fracture.* This is one in which the skin or mucous membrane is so lacerated that there is direct or indirect communication between the fracture and external air. The skin is broken and the bone is usually seen to protrude.

3. *Comminuted* — a fracture in which the bone has broken into more than two pieces.

4. *Complicated* — a fracture in which important structures such as arteries, nerves or joints are involved or damaged.

5. *Multiple* — a condition where more than one fracture exists.

6. *Impacted* — a fracture in which one fragment is driven into the other.

(ii) *Incomplete*—

1. *Green-stick.* Here the fracture merely involves the convexity of the curve whilst the concave half is bent. It occurs only in young children and most often in those that are rickety.

2. *Depressions* — as seen in the skull, where the outer table of bone is driven in without fracture and the inner table alone splintered.

3. *Fissured.* These often are only partial.

4. *Subperiosteal.* This is one in which the periosteum remains intact although the bone is broken.

Signs

The signs of a fracture are several but it must be remembered that not every sign

listed below is necessarily present—there may only be one or two signs, depending on the bone involved and its method of production. The following list will give you a general outline of the signs, namely:

1. *Signs of local trauma* — (a) pain, bruising, swelling; (b) blebs, bullae; (c) inflammation may be present with all its cardinal signs.

It is wise to remember that these signs can easily camouflage an underlying fracture. Many legal cases have been brought against the inexperienced doctor who overlooked such a case.

2. *Preternatural mobility in continuity of the bone.* This sign is discovered by manipulation, but never unnecessarily. If there is impaction or non-separation of the fragments, this sign is not demonstrable.

3. *Partial or complete loss of function.*

4. *Crepitus.* It is a wise thing for the young future doctor to realize at this time that in the majority of cases it is unwise to attempt to demonstrate this sign, for many simple fractures have been turned into complicated fractures and, again, the procedure usually causes the patient extreme pain. If present, however, and easily demonstrated, it is a specific fracture sign. It cannot be felt where the fragments are impacted or widely separated.

5. *Deformity from displacement.* This sign is the result of

(a) the direction of violence,
(b) gravity acting on the limb, i.e. the weight of the limb,
(c) muscle shortening,
(d) haemorrhage and inflammatory oedema.

It is greater in the fractures due to indirect violence, e.g. the oblique and spiral types. The various types of deformities are, namely:

(a) Angular — commonest in unequal muscular action.
(b) Lateral — commonest in the transverse type.
(c) Longitudinal—this can be shorter or longer.
(d) Rotatory.
(e) Depression or Elevation.

General Effects

Besides the local signs above, the patient is also subject to several effects. In the main these are, namely:

1. *Shock.* Its severity varies with the character of violence, seat of injury, and the amount of pain due to the accident and resultant treatment.

2. *Haemorrhagic.* Haemorrhage is rarely sufficient to give any effects unless the fracture is open and involves some important vessel.

3. *Fever.* In uncomplicated cases an aseptic traumatic fever may occur in twenty-four hours and last forty-eight or seventy-two hours. It rarely exceeds 100° F.

4. *Traumatic delirium*—
(a) Active,
(b) Low muttering, or
(c) Tremens.

5. *Fat embolism.* This is a very important effect to remember as a cause of death soon after fractures in a small number of cases.

Complications

The complications can occur as the result of the fracture before or during the following treatment:

A.—*Before treatment*

1. *Implication of a joint.* There is no permanent harm if the fragments are in perfect apposition; if not in perfect apposition, harm results due to adhesions and so on.

2. *Dislocation in a neighbouring joint.*

3. *Injury of the main artery.* This may be compressed, contused, or punctured to

give thrombosis, aneurism, or haemorrhage. The thrombosis may lead to a dry gangrene and the haemorrhage may lead to a moist gangrene.

4. *Laceration of veins.* This leads to haemorrhage.

5. *Injury of nerves.* The injury may occur immediately or secondarily from its inclusion or compression in the resulting callus.

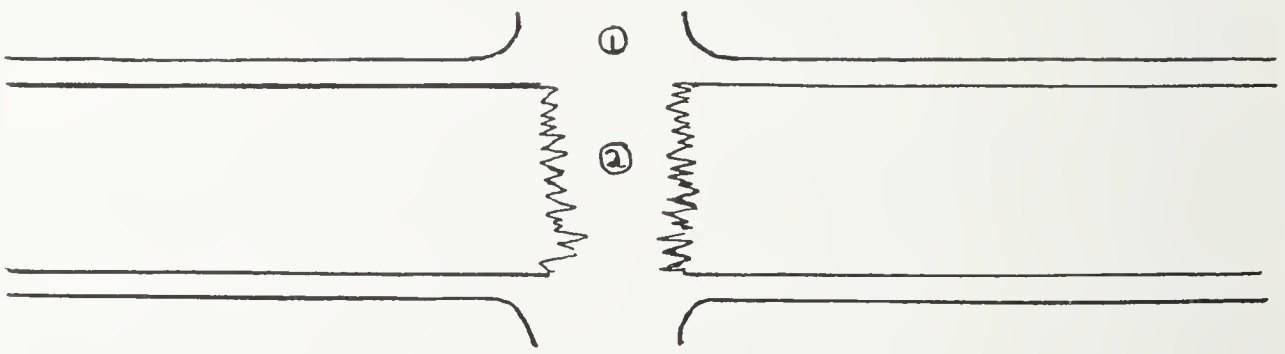
B.—*During treatment*

1. *Hypostatic pneumonia.* A condition most frequently seen in the aged who are confined to long terms in bed.

2. *Bed-sores.* Also a condition most frequently seen in the aged who are confined to bed.

3. *Crutch palsy.* This is due to compression of the brachial nerves.

4. *Volkmann's Contracture.* In this condition the fingers are flexed and



clawed and the wrist is hyperextended. It is due to necrobiosis of the muscular tissue from the deprivation of blood, due to pressure of a splint or bandage and followed by a spreading myositis fibrosa.

5. *Myositis ossificans.* A condition where bone forms in the muscle.

6. *Gangrene.* This can occur from errors in treatment, e.g., too tight bandages.

7. *Splint sores.* This is a form of localized gangrene due to a bad splint.

Before continuing with a general outline of treatment, I shall first present a very brief description of the constituents of normal bone and what occurs in the case of a fracture. The living elements of bone are, namely:

1. *Blood vessels*—
(a) nutrient periosteal vessels;
(b) nutrient artery to the medullary cavity.

2. *Bone cells*—
(a) Adult bone cells in the lacunae—the osteocytes—potentially they are mature and incapable of producing osseous matrix.
(b) germinal cells lining the medullary cavity, outside of the bone, and also the Haversian canals—the osteoblasts—potentially capable of forming osseous matrix and mature bone cells.
(c) Osteoclasts. These are cells which deal with the absorption of bone.

3. *Inorganic salts*—
(a) Calcium carbonate.
(b) calcium phosphate.

When a fracture occurs the periosteum may or may not be torn. If torn, the periosteum is stripped back and the neighbouring small vessels are pulled out of their canals. The blood vessels are also injured and torn, with the result that necrosis will occur at the site supplied and also a haematoma.

Healing of Fractures

I shall deal with a fracture which is well-reduced and under ideal circumstances.

First, I wish to say that fractures heal in the same manner as any wound of soft tissue, i.e. by granulation tissue.

Immediately following the fracture, there occurs a proliferation of capillaries and osteoblasts into the blood clot to form

granulation tissue or the soft callus. The soft callus is divided into two parts, (1) the ensheathing callus, (2) the central callus (see diagram). At the same time this process is occurring, the osteoclasts remove any dead bone and free the calcium salts. This later process is termed "Rarefying Osteitis." The next step in healing is a secretion of osteomucin by osteoblasts. Calcium salts are now deposited from the blood in the capillaries and the "hard callus" is formed. The osteoblasts are now surrounded and tend to form fine minute Haversian canals and also small spaces called lacunae for the cell body. The bone cells, i.e. the osteoblasts, are now mature and take up their new position in the lacunae as osteocytes. The osteoclasts again function in that they remove any excess bone, i.e. the ensheathing bone. The fracture is now healed.

Treatment

The general outline of treatment is seen below, namely:

1. *Reduction of deformity*—
2. *Prolonged extension*—

(a) The force to overcome acting muscles, e.g., 10-20 pounds in the case of the thigh muscles of a muscular adult;

(b) sufficient grasp is required for good and prolonged extension. This can be done by (i) adhesive plaster—Buck's extension; (ii) skeletal traction by means of a Kirschner wire and spreader; (iii) ice-tong calipers.

Before continuing, I wish to compare the advantages and disadvantages of Buck's extension and skeletal traction.

Buck's Extension—

I.—Advantages:

1. Universally applicable.
2. It does not require much supervision.
3. There is little or no danger of infection.

II.—Disadvantages:

1. It immobilizes the distal joints.
2. The maximum load it can carry is 25 pounds.
3. Ulcers occur if it is applied too long.
4. Patients with oily, pimply skin get skin eruptions which necessitate removal.

Skeletal Traction—

I.—Advantages:

1. It is applied directly to bone and controls the distal fragment better.
2. It will take a load of almost any amount.
3. There is no time limit for its use.

II.—Disadvantages:

1. It requires constant supervision.
2. There is danger of infection along the wire to give an osteomyelitis.
3. There is a mechanical difficulty to overcome; i.e. the wire must pass through the bone at a right angle or the resulting reduction is poor.
4. Pressure necrosis of the skin may occur under the wire.

(c) Fixation.—This can be carried out by

(i) Splints or

(ii) Fixed apparatus, such as starch or Plaster of Paris.

(d) Operative treatment. Bone fixation is carried out by the following means, namely:

(i) Silver wires—Kirschner.

(ii) Screws, nails, pegs of bone.

(iii) Intramedullary pegs.

(iv) Lane's Plates for long bones.

(v) External means, e.g., the newly tried Stader Splint.

(e) Massage and mobilization. These should be carried out as soon as

possible to keep the muscles and joints in a good state of health.

(f) Ambulatory treatment. This consists of the use of walking casts.

In conclusion there are a few beneficial points, which I might refer to, dealing with the ideal circumstances for healing, normal healing times for certain bones, signs and causes for un-united fractures, etc.

Ideal Circumstances for Healing

These circumstances are as follows, namely:

1. Perfect reduction or apposition. There must be no interviening fragments. This results in the formation of a minimum of callus.
2. Perfect immobilization. Accomplished by the use of proper splints.
3. Good circulation. Important for the vitality of the distal fragment.
4. Age. Healing occurs more rapidly in the child than in the adult.
5. General good health.
6. The absence of sepsis, tumor, and so on at the fracture site.
7. Good cellularity at the fracture site.

Causes of Ununited Fractures

These causes are the opposite circumstances as listed above under ideal circumstances, namely:

1. Want of apposition of the fragments due to extensive resection or muscular action.
2. Interposition of muscular or aponeurotic tissue or detached fragments of bone.
3. The failure of efficient reduction and its maintenance.
4. Defective blood-supply to one or both fragments due to the injury of the nutrient artery.
5. Local affections of the bone:—(a) suppuration; (b) necrosis; (d) tumor (malignant); (d) undue pressure on the callus.
6. General bone disease — osteomalacia and rickets.
7. General constitutional weakness or debility and certain diseases—(a) scurvy; (b) severe syphillis.

Signs of Ununited Fractures

Ununited fractures may be diagnosed by three main signs, namely:

1. Movement, passively or actively, at the site.
2. Pain on torsion at the site.
3. X-ray results.

When a Cast is to be Removed

A cast is removed under normal or abnormal signs and symptoms as seen below, namely:

1. When the fracture is healed.
2. In the presence of edema.
3. In the event of muscular atrophy.
4. In the event of bone atrophy.
5. When the cast-off dead skin can not escape and leads to marked irritation and discomfort.
6. In the presence of cast sores.

Healing Times (Normal) for Certain Bones

Individual bones vary in their normal healing time. Some of the more important healing times are, namely:

1. Shaft of the femur—10-12 weeks.
2. Shaft of the tibia—8-10 weeks.
3. Shaft of the humerus—6-8 weeks.
4. Shafts of the radius and ulna—10-12 weeks.

Reasons for a Stiff Joint

Stiff joints are sometimes seen as the result of fractures and below are a few points which are the cause of such a condition, namely:

1. Shortened muscles.
2. Loss of capsule elasticity.

3. Scar formation in the folds of the capsule due to organization of haemorrhage, fibrin, and edema here. (There will be no adhesions in a joint if the capsule remains intact.)

Operative Treatment

In operative treatment it must be remembered there are common sites of operation, advantages of operative treatment, and finally disadvantages of operative treatment.

A.—*Common sites of operative treatment—*

1. Patella fracture.
2. Olecranon facture.
3. Neck of the femur.
4. Bones of the forearm, namely the radius and ulna.

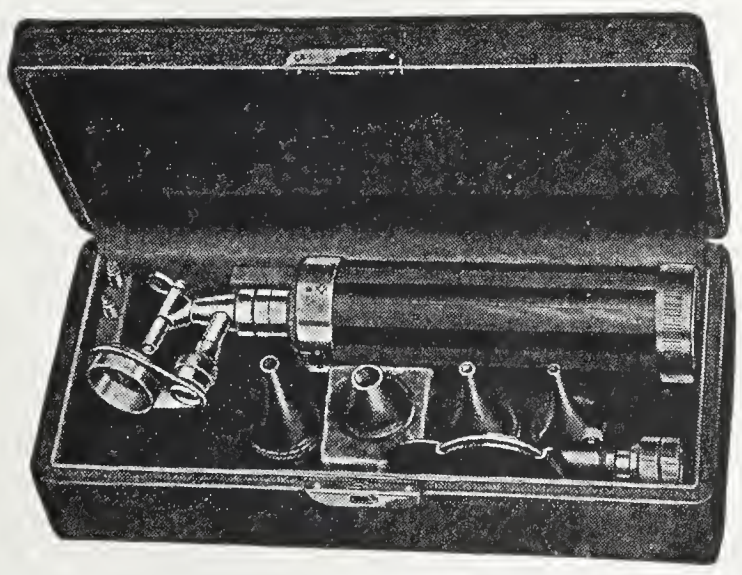
B.—*Advantages of operative treatment—*

1. Excellent reduction.
2. Complete immobilization.
3. Bony spicules and haemorrhage can be removed.
4. It is the only way to treat the fractures listed above in "the common sites."

C.—*Disadvantages of operative treatment*

1. Danger of infection.
2. Destruction of the blood supply, especially in the long bones.
3. Injury to the surrounding tissue, with scar formation the result.

This concludes the discussion of "Fractures in General." Individually, special fractures, each has its own method of production, deformity, signs, and treatment, but it is another topic of discussion. I have outlined general principles in the hope, as I have stated above, that the newcomer to clinical surgery may get a firmer grasp on this important division of surgery.



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HEADACHES—PART II*

TREATMENT

C. T. COLLINS-WILLIAMS, B.A., 4T4

Headache is such a complex subject and part of the symptomatology in so many diseases, that a complete discussion of its treatment is impossible in a paper of this length. For this reason, the discussion of treatment will be limited mainly to migraine with only brief reference to other types.

Migraine

In a case of suspected migraine the first step should be a thorough history and examination in order to find out the contributing or causative factors. Because the syndrome may be closely simulated by other disorders, its diagnosis must often be largely one of exclusion.

The main thing in treatment is to get the patient into the very best of condition, both mentally and physically. The patient should lead as quiet a life as possible, shorten his hours of work, increase his hours of recreation and sleep, and resign some of his responsibilities. Psychotherapy is often helpful. The patient should also restrict his use of alcohol and tobacco. During an attack rest in bed in a dark room is helpful. If the patient is in good physical condition, his response to drugs is better.

By far the most useful drug for the relief of migraine is ergotamine tartrate. This is made from the mould which grows on spoiled grain. Its use for the relief of migraine was first reported by Maier in 1926 and was first introduced onto this continent in 1934. That its action is specific and not merely that of a pain sedative is proved by the fact that non-migrainous headaches are not ordinarily benefitted by it.

Ergotamine tartrate was first used in the belief that it would abolish spasm of the cerebral arterioles since it inhibits the vasomotor action of adrenaline and its chief effect is paralysis of the motor sympathetic. Actually its action is to constrict the branches of the external carotid artery. It has no effect on the pial or cerebral vessels.

The drug may be given orally, subcutaneously, or intravenously. Subcutaneously, it will relieve 90% of cases in 15 to 45 minutes. On first treatment a trial dose of 0.5 mgm. should be given. If this does not control the headache after two to three hours the dose should be repeated. In subsequent attacks if repetition was necessary 1.0 mgm. should be given as an initial dose. Not more than this amount should be injected at one time, and no more than two injections should be given in a day. If these do not improve the condition, additional doses will probably be of no use anyway.

Orally, a single dose of 1 to 2 mgm., repeated every hour, up to a total of 6 mgm. may be given. This method is no good when vomiting is part of the syndrome. The drug is poorly absorbed from the intestinal tract. No more than 6 mgm. should be given in a day and no more than three such quantities in a single week. If the tablets are crushed and allowed to dissolve beneath the tongue, their effect is more rapid and more complete than when ingested. But many patients do not

**Presented to the Alpha Omega Alpha Society, May 3rd, 1943, at the home of Dr. Fletcher McPhedran, Toronto.*

like the taste. Oral administration is effective in 40% to 70% of cases.

The intravenous method is rarely needed and should be used only by those thoroughly familiar with the action of the drug. Not more than 0.25 mgm. in a single dose and not more than two doses per day should be given.

The drug must be given within half an hour from the beginning of the headache to be of any use. Atropine sulphate, 1/100 to 1/50 gr. per os or by injection, helps to relieve the nausea and vomiting which results from the increased pyloric tone due to the ergotamine tartrate. Without atropine, the vomiting may be so severe that the patient prefers the headache to the vomiting.

It is pretty generally agreed that daily doses as a prophylactic against attacks should not be given, because of the danger of ergotism. Properly controlled doses lead to no bad effects. It gives great relief during attacks but has no effect on their frequency. The dose does not need to be increased with the passing of time.

It is important that the patient should lie down for one to two hours after medication to assist the drug and to diminish the symptoms of overaction of the drug. These symptoms are nausea, vomiting, muscle pains, weakness of the legs, stiffness of the joints, a sense of constriction in the throat, heaviness in the chest, and burning and tingling of the fingers and toes. Ten c.c. of 10% Ca gluconate solution intravenously diminishes the muscle pains.

Untoward effects may occur from the use of too large doses, from small doses in individuals showing an idiosyncracy to the drug, or from the use of usual doses apparently due to the cumulative effect of the drug. The sensitivity of individuals varies widely. Some patients take the drug in the usual doses over periods of weeks and even months without untoward symptoms developing, others require 2 or 3 times the usual dosage if therapeutic results are to be obtained; and still others develop symptoms of ergotism following only small doses of the drug.

Both the physician and patient must be aware of the toxic manifestations. The earliest symptoms of ergotism are headache, nausea and vomiting, diarrhea, tinnitus, and vertigo. There are also many much more serious toxic manifestations.

If the symptoms of poisoning appear, the following steps should be taken:

1. Stop the drug.
2. Inject 1 c.c. of 1% solution of pilocarpine subcutaneously since this has a fast dilating effect.
3. Give a daily intravenous administration of 15 to 20 c.c. of 3% $MgSO_4$ solution.
4. Give cleansing enemas when ergotamine has been given orally.
5. Administer alcohol orally.

The pathological changes associated with ergotamine tartrate poisoning are vasospastic obliteration of the arteries, intimal edema and hyperplasia, hyaline degeneration and thickening of the vascular walls, lymphocytic infiltration and frequent thrombosis.

These changes suggest the contraindications to the use of ergotamine tartrate. These are:

1. Sepsis, since then two conditions capable of producing intimal damage and thrombosis are active simultaneously.
2. Cardiac disease, particularly with obliterating vascular disease of the coronaries.
3. Vascular disease, particularly of the obliterative type. Also, the treatment should be continued with caution in the presence of:
   (i) Hepatic disease.
   (ii) Renal disease.

(iii) Vitamin C deficiency.

(iv) Hypersensitivity to the drug.

Ergonovine produces fewer unpleasant symptoms than ergotamine but also is less effective in stopping the pain. It is contraindicated during pregnancy because of its strong oxytocic action. The dosage and method of administration are the same as for ergotamine. It is readily absorbed from the gastrointestinal tract.

A great many investigators have attributed attacks of migraine in certain people to allergy. However, it must be emphasized that the allergic aspect of migraine is not generally accepted and that the importance that some people attribute to it is due to the fact that migraine lends itself very readily to speculative treatment. In spite of this, the volume of literature on the subject justifies a brief summary of allergy in migraine.

The allergic aspect warrants investigation in children with migraine and in patients with a strong hereditary background of allergic tendencies and personal susceptibility to other allergic disorders. Allergy to known foods has precipitated migraine in a not inconsiderable number of cases. Allergens can provoke the vasodilatation responsible for the headache.

When a case falls in the allergic group, the offending allergens must be identified and eliminated. The individual is carefully tested by both scratch and intradermal methods. Such cases show less pronounced immediate positive reactions than we find in those cases with respiratory tract or dermal sensitizations, so the intradermal test is more likely to give the more accurate insight into the patient's sensitivity. Both immediate and delayed reactions must be observed for accuracy. But dietary experimentation often proves that substances which give doubtful or even negative skin tests are responsible for attacks so it may be necessary to test the individual by eliminating certain foods from the diet. The inhalants are relatively unimportant in migraine.

The leucopenic index may give useful information. Normally, food causes a rise in the leucocyte count, but a food to which a person is sensitive will cause a drop of 1000 or more in the count. This test is still in the experimental stage.

The specific treatment is to avoid the offending allergen. Nonspecific desensitization with peptone has met with success in some cases, and desensitization with histamine has been successful in a few cases.

A great deal of work has been done on migraine associated with menstruation. Both Sodium Bromide gr. 15 three times a day and Fluid Extract of Cannabis 5 drops three times a day increased daily by one drop up to 11 drops three times a day are claimed to be effective when given from three days before the onset of the period to three days after the onset. Antuitrin-S, in doses of 100 to 200 rat units injected at the onset of the attack or three times a week to prevent the occurrence of attacks; the gonadotropic extract of pregnancy urine; emminin, in doses of 2 drachms daily increased to 4 drachms before the menstrual periods are also used. Many workers claim that artificial induction of the menopause is indicated in this type of migraine.

Progynon-B in doses of 10,000 to 20,000 I.U. per day is claimed to be effective in women who are ovariectomized, past the menopause, or otherwise show evidence of ovarian hypofunction.

Dilantin is effective in certain cases. It is not hypnotic. Capsules of 1½ gr. may be given every hour for four hours. If there is no improvement by this time, there is no use continuing with the drug.

Of the sedatives, the best is phenobarbital (luminal) 1 gr. every night. If

given for the ten days before an attack is expected, this may be helpful. Codeine should be used only in rare instances and morphine should never be used for migraine.

There are many cases of complete or marked relief upon inhalation of 100% oxygen, even in cases in which ergotamine tartrate is of no help. This has none of the annoying side reactions that often accompany the use of ergotamine. The usual rate of administration is 6 to 8 liters per minute. The oxygen is much more effective in migrainous than in non-migrainous headaches.

Experimentally, it has been shown that potassium thiocyanate is usually effective in relieving migraine when associated with hypertension and may be effective also in relieving migraine in some instances when the blood pressure is within the commonly accepted "normal" range.

There are many other substances which have been used to treat migraine. Reasonably good results are claimed for vitamin B, trichlorethylene, chondroitin sulphuric acid, duodenal lavage with 30 c.c. of 33% magnesium sulphate, a ketogenic diet, calcium lactate, and benzyl benzoate. This long list of palliative measures emphasizes the severity of migraine and the elusiveness of the underlying principles which may lead to a cure.

Serious attempts at a surgical treatment have been made but these should be resorted to only if less drastic measures fail.

A logical procedure for the one-sided headache is to strip the external carotid artery of its nerves. The operation has been carried out too seldom to permit evaluation of it.

Surgical procedures have been more successful in the treatment of migrainous neuralgia, a form of migraine or unilateral headache which mostly affects the front of the head on one side around the eye, temple and upper jaw, occasionally spreading to the back of the head and only rarely to the lower jaw. This differs from ordinary migraine in the absence of the preliminary warnings and in the rarity of nausea or vomiting. Patients have often suffered from typical migraine in childhood or migraine may be frequent and severe in other members of their families.

The various procedures adopted to treat this depend on the distribution of the pain, and are:

1. Alcohol injection of the infraorbital or supraorbital nerves, or division of the same nerves.
2. Alcohol injection of the Gasserian ganglion.
3. Division of the inner 1/3 of the trigeminal root.
4. Division of the inner 1/3 of the trigeminal root with division of the maxillary nerve at the foramen rotundum.

In conclusion, it should be emphasized that there are a great many drugs which are used to relieve attacks of migraine, and of these, ergotamine tartrate is the most effective. But for good results with any of the drugs, the all important thing is to have the patient in the best possible mental and physical condition. To bring this about is at present the most effective treatment of migraine.

Headache due to an expanding intracranial lesion

The most common lesion of this sort is a tumour and when the tumour can be removed the headache need not be treated. However, when the tumour cannot be removed a palliative subtemporal decompression, ventricular or spinal punctures and analgesic medication will usually control the headache itself. It is important for diagnosis to remember that this type of headache may be relieved by aspirin.

Headache due to cerebral edema

If the edema is due to overindulgence in alcohol, 10 mgm. of benzedrine sulphate by mouth is probably the best treatment, but phenacetin and caffeine are also useful. Lumbar puncture is also used.

Headache immediately following cerebral concussion, contusion, or laceration, with or without fracture of the skull, requires very careful treatment. Absolute bed rest for a period of a few to twenty-one days depending on the severity of the injury is essential. The advisability of limiting the fluid intake to 800 to 1200 c.c. per 24 hours is controversial. Repeated spinal punctures until the fluid clears or until the cerebro-spinal fluid pressure is under 200 mm. H_2O are advisable. However, if the patient is unconscious after the injury, spinal fluid should not be drawn except for diagnostic purposes until the third day. From that time onward, if the patient complains of headache the slow withdrawal of three-quarters of a test-tube of fluid is indicated. This often gives marked relief and if it does so it should be repeated twice a day until the fluid clears on or about the seventh day. Intravenous hypertonic solutions are frequently of value in the same condition. Glucose, 100 c.c. of 50% solution every few hours, is the most frequently used but sucrose may be of still greater value. Such solutions produce only a very temporary effect.

In the treatment of headache due to intracranial lesions it is dangerous to use analgesics that produce depression of the medullary centres. Opium and its alkaloids are contra-indicated despite the ineffectiveness of other measures.

Post-traumatic concussion headaches

It is felt that a great many of these can be avoided by suitable treatment at the time of injury. In many cases psychotherapy alone may be effective treatment. In other cases when the compensatory angle of the case is settled the headache disappears. Small doses of sedatives such as luminal gr. ½ and sodium bromide gr. 5 taken together three times a day may be effective.

In cases where the headache is caused by a chronic increase of intracranial pressure due to subdural collections of fluid or subdural hematomas produced at the time of accident and persisting or increasing due to continuing fluid imbibition the headache is relieved only by trepanation.

In those cases where the headache is due to inadequacy of the systemic circulation when the patient assumes the erect posture after having been confined to bed for a head injury, graded exercises in the horizontal position and gradually increasing to sitting-up exercises and walking should be used. In this type of case, the injection of 1 c.c. of 1 in 2000 solution of prostigmine methylsulphate intramuscularly twice weekly and a 15 mgm. tablet of prostigmine bromide three times a day by mouth is claimed to bring about many cures. The rationale of this treatment is that prostigmine dilates labyrinth and cranial blood vessels.

If the headache is caused by continuing traction between the brain and some sensitive area of the dura, air should be introduced into the subdural space either through a trephine hole at the site of maximum pain or by spinal insufflation, at the same time as the ventricles are being drained of all fluid so that the brain collapses and pulls away from the dura.

If the headache is due to chronic edema, dehydration treatment is necessary.

Headache due to hypertension

This type of headache may be alleviated to some extent by the nitrites, barbiturates, and analgesic drugs, alone or in combina-

tion. Greatly limited mental and physical activity is desirable. Relief is sometimes obtained by the use of high pillows at night. Warm baths are often effective. In properly selected cases of malignant hypertension, bilateral extensive sub-diaphragmatic sympathectomy will effect complete alleviation of the headaches.

Headache due to cerebral thrombosis and arteriosclerosis

Analgesic drugs offer little, and even codeine may fail to control it. If there is concomitant hypertension, vasodilating drugs or large doses of sedatives may alleviate it to some extent.

Post-puncture headache

This can often be prevented by the patient lying on his face for 12 hours after a lumbar puncture. The forcing of fluids up to 2500-3000 c.c. for 24 hours following the puncture seems to have at least empiric value. The usual analgesic drugs have some beneficial effect.

Headache due to refractive errors

The only treatment necessary is correction of these errors.

Menopausal headache

Oestrin often produces excellent results. The dose varies from patient to patient, but 15000 I.U. per day may be used to start with. Stilboestrol, ½ mgm. or less per day, is often effective also. The injection of 1 c.c. of antuitrin-S once a week for six weeks or so will often produce most gratifying results. In all cases, the minimum dose that will produce the required result should be used.

Headache due to toxemia

Relief may be obtained by sedatives while the toxemia is being treated.

Headache due to sinus disease

The treatment for this is adequate drainage of the sinus. This can often be accomplished medically by carefully shrinking the mucosa at the entrance to the sinus by the use of aqueous ephedrine or some such substance. In some cases, operative drainage may be necessary, but this should be resorted to only after all other possible causes of the headache have been eliminated.

Headache due to the teeth

The treatment is removal of the teeth responsible, e.g. impacted molars.

Psychoneurotic headache

The main treatment of this is to take a careful history, partly for the patient's benefit and to help the patient to understand the conflict or maladjustment immediately responsible for the symptoms and how it can give rise to the symptoms. When the precipitating factors cannot be discovered, aspirin or a combination of aspirin, phenacetin and caffeine may be effective but in many cases drugs are of no use.

Indurative or nodular headaches

In this type of headache treatment is often successful but persistence is necessary. The application of heat and particularly deep long-continued massage are often followed by recovery. Massage must be given daily. For the first ten to fourteen days it may produce an increase in the headache, but afterwards the condition tends to improve and disappear.

Large doses of salicylates combined with sodium bicarbonate are often useful. The injection of the tender spots with 10 c.c. of 1% novocaine often produces a cure.

Histaminic cephalgia or Erythromelalgia

Before treating this type of headache the diagnosis should be confirmed by

inducing an attack with a subcutaneous injection of 0.1 to 0.2 mgm. of histamine. Induced attacks seem identical to spontaneous attacks. It is never possible to induce attacks of this character by giving histamine to a normal person.

For treatment histamine diphosphate is injected subcutaneously twice daily. The first injection is 0.25 c.c. of a solution containing 0.275 mgm. of histamine diphosphate per c.c. At each subsequent injection the dosage is increased by 0.05 c.c. to a maximum dose of 1.0 c.c. In all, twenty injections are given. If at any time the patient notices slight flushing of the face or any other symptoms indicating subjective or objective response to the drug, the next dose should be reduced by 50% and then increased gradually again. Further attacks may be prevented with approximately 1 c.c. of the drug one to three times a week. A few patients do not require a maintenance dose.

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THE MEAD JOHNSON VITAMIN B COMPLEX AWARD

Nominations are solicited for the 1944 award of $1,000 established by Mead Johnson and Company to promote researches dealing with the B complex vitamins. The recipient of this award will be chosen by a committee of judges of the American Institute of Nutrition. The award will be given to the laboratory (non-clinical) or clinical research worker in the United States or Canada who, in the opinion of the judges, has published during the previous calendar year January 1 to December 31 the most meritorious scientific report dealing with the field of the B complex vitamins. While the award will be given primarily for publication of specific papers, the judges are given considerable latitude in the exercise of their function. If in their judgment circumstances and justice so dictate, it may be recommended that the prize be divided between two or more persons. It may also be recommended that the award be made to a worker for valuable contributions over an extended period but not necessarily representative of a given year. Membership in the American Institute of Nutrition is not a requisite of eligibility for the award.

To be considered by the committee of judges, nominations for this award for work published in 1943 must be received by the secretary, Arthur H. Smith, Ph.D., Wayne University College of Medicine, Detroit, by January 10, 1944. The nominations should be accompanied by such data relative to the nominee and his research as will facilitate the task of the committee of judges in its consideration of the nomination.

Abstracts

JACK LAIDLAW, Editor

Contributors

Donald Fraser
C. W. J. Armstrong
W. B. Spaulding
Harold Kalant
K. M. Johnston
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MEDICINE

The Action of Specific Stimulators on the Haematopoietic System

By Franklin R. Miller and D. L. Turner
Amer. Jour. of Med. Sci.,
206: 146-158, 1943

Previous work by Miller et al. has shown that it is possible to produce a proliferation of lymphoid or myeloid tissue in animals by the injection of different fractions of extracts from the urines of leucaemic patients. The concentration of the active principle in each stage of the separation was estimated by the injection of a sample into an animal with subsequent examination of the intensity of the response by the leucocyte-forming tissues. The specific substance in the lymphoid stimulating fraction is believed to be a hydroxy acid, and that in the myeloid stimulating fraction to be keto acid. It has been possible to convert chemically (by oxidation) the lymphoid into the myeloid principle, and vice versa.

This paper deals with a study of the lesions produced in a large series of animals by injections of extracts from the urines of patients suffering from each of: myeloid leucaemia (chronic and acute), lymphatic leucaemia (chronic and acute), lymphosarcoma, monocytic leucaemia and Hodgkin's disease. Guinea pigs, each injected with a concentrate of one of the various urines, were sacrificed when moribund and their tissues examined. A summary of some of the findings follows:

Source of Urine Extract	*Histological Findings*
(1) Chronic myeloid leucaemia	Myeloid proliferation in liver, spleen, adrenal and bone marrow; no lymphopoiesis in spleen.
(2) Acute myeloid leucaemia	Same as (1).
(3) Chronic lymphatic leucaemia	Spleen and lymph nodes enlarged; lymphoid hyperplasia.
(4) Acute lymphatic leucaemia	Same as (3); changes sometimes more marked.
(5) Lymphosarcoma	Lymphoid hyperplasia.
(6) Monocytic leucaemia	Response neither lymphoid nor myeloid; lymph nodes enlarged; increased megakaryocytes.
(7) Hodgkin's disease	Same as (6), but more lymphoid.

The blood changes were not found to be of special significance. Simultaneous injection of equal amounts of lymphoid and myeloid stimulating fractions gave results similar to the Hodgkin's and monocytic leucaemia extracts.

By separation procedures it was found that both the myeloid and lymphoid

stimulating principles were present in the urines from nearly all of the seven types of patient mentioned. The presence or absence of the specific substances in the urines together with a rough estimate of their relative activities, as found by experiment, is indicated below:

Urine Source	*Lymphoid Activity*	*Myeloid Activity*
Chronic myeloid	+	+++
Acute myeloid	—	++
Chronic lymphatic	+++	+
Acute lymphatic	+++	—
Monocytic leucaemia	++	+++
Hodgkin's disease	+++	++

This work suggests that there are only two specific stimulating substances involved in the production of the histological changes described; one stimulates myeloid proliferation, and the other stimulates lymphoid proliferation. The authors propose a theory which explains the occurrence of leucaemia and allied diseases on the basis of the relative concentrations of the two specific stimulating substances in the animal body. The paper is illustrated with twenty photomicrographs.

C.W.J.A.

Thiouracil in the Treatment of Thyrotoxicosis

By R. H. Williams, M.D., and
G. W. Bissell, M.D.

New Eng. J. Med. 229; 97-108; 1943

It now appears certain that we are on the threshold of a new era in the therapy of thyrotoxicosis. This had its origin in the observation by Mackenzie, Mackenzie and McCollum that the feeding of sulphonamides to rats was followed by thyroid enlargement with hyperplasia of the acinar cells and a decrease in follicular colloid. There was an accompanying drop in the basal metabolism. Further study showed that other sulphur-containing compounds, notably thiourea and its derivatives had a similar action. Astwood found that of these substances 2-thiouracil had the greatest goitrigenic activity and used it on 3 thyrotoxic patients with lowering of the basal metabolism and remarkable clinical improvement.

The above authors report 9 cases of thyrotoxicosis treated with thiouracil. These patients also received supplemental vitamins, and sedatives at night. None were confined to bed. Some were treated in hospital; others were ambulatory.

In all cases clinical improvement appeared within several days and progressed continuously until, after 4-7 weeks all thyrotoxic symptoms were gone. A gain in weight usually occurred by the third week and was most rapid during the fourth and fifth weeks. The metabolic rate fell progressively to values within the normal limits and stayed there so long as thiouracil was given. The response of the thyroid gland varied. In all cases its firmness gave way to softness. In 3 cases definite enlargement occurred with subsequent return to the original size; in 2 cases there was regression to normal size; the rest showed some decrease in size. Blood iodine studies on 4 cases demonstrated a fall of the protein-bound iodine to normal or subnormal levels.

Pharmacology, Treatment and Complications:

Thiouracil is rapidly absorbed and excreted. When 0.2 gm. is injected every 4 hours a blood level of 3 mg. % is reached after 24 hours and this remains constant with a daily urinary excretion of about 300 mg. Almost all the drug is contained in the blood cells, the concentration is the white cells being many times that in the red cells, although the amount contained in the latter is greater. The bone marrow, adrenal and pituitary glands take up more of the drug than other tissues, including the thyroid gland.

The optimum dose for therapy remains to be determined. The authors recommend 0.2 gm. of thiouracil each 4 hours five or six times a day until moderate clinical improvement and a fall in basal metabolism occurs when medication is reduced to three to four times daily. Once the metabolic rate becomes normal 0.2 gm. is given once or twice daily. It is necessary to maintain the patient on this dosage for discontinuance of the drug is apt to be followed by a recurrence of the disease. There has yet to be determined how long this maintenance dose must be given before it can be stopped without causing a recurrence.

The single complication so far noted has been an agranulocytosis in a patient receiving 2 gm. daily. No change in the white count was observed in the above series. Two patients showed a brief pitting edema with elevated serum chloride and slight fall in the carbon dioxide combining power which disappeared spontaneously in the face of continued therapy. Another case developed a transient swelling of the submaxillary glands.

Mechanism of Action:

The weight of present data suggests that thiouracil acts by inhibiting the production of thyroid hormone by the gland itself. It does not affect the stimulating action of ingested thyroid or injected thyroxine on the metabolic rate of animals. Neither does it affect the subnormal metabolism of myxedematous patients nor inhibit their response to thyroid extract. In a single case, when given with thyrotropic hormone, the thyroid gland did become larger and firmer, yet there was no increase in the metabolic rate, rather a slight fall, suggesting inhibition of hormone production. Thiouracil had no affect on the metabolic rate of a case of colloid goitre.

Summary:

Thiouracil is a drug which effectively eliminates the toxic manifestations of hyperthyroidism and reduces the basal metabolism to normal. It gives promise of being a medical means of carrying the patient through the active phase of thyrotoxicosis into the period of natural remission of the disease.

J. R. Stern.

The Oral Use of Sulphathiazole as a Prophylaxis for Gonorrhoea

By Capt. J. A. Loveless and
Col. W. Denton
Medical Corps, Army of the United States

Ref. J.A.M.A., Mar. 13, 1943, p. 827

Following reports by two United States navy groups on the successful use of sulphathiazole immediately after exposure to venereal disease, the United States has published this preliminary report for a larger group, on the value of sulphathiazole as prophylactic agent.

Four thousand negro soldiers were designated to the control group, and about one thousand four hundred to the test group.

Those in the test group, on signing

out of Fort Benning, were required, under N.C.O. supervision, to swallow 2 gms. of sulphathiazole each time. These men also received 2 gms. routinely on signing in that night, and another 2 gms. next morning. The cost of such a routine prophylactic procedure is only about 10 cents for each man per month.

The results obtained for a five-month period are as follows, neglecting, in the test group, all those who did not adhere absolutely to the predetermined routine.

Control Group	*Test Group of Prophylactic Sulpha*
Syphilis—	
59 cases/1000 soldiers/annum	39 cases
Gonorrhoea—	
170 cases/1000 soldiers/annum	7 cases
Chancroid—	
64 cases/1000 soldiers/annum	5 cases

These results are outstanding. As is to be expected, the incidence of syphilis is not significantly altered, considering the relatively small number of soldiers in the test group. However the rate for gonorrhoea was decreased to 4% of its usual incidence, and the rate for chancroid to 8% of its former incidence.

The men were very carefully observed for evidence of toxic, allergic or sensitivity reactions. These reactions were limited to the occasional mild and not incapacitating spell of nausea, and in all the cases, despite the frequently repeated dosages, no evidence whatever of sulphathiazole sensitization has occurred.

The workers feel that, until further investigation of the development of sensitization is complete, the routine should not be generally adopted. But they feel convinced, despite the inevitable dangers in such a mass administration of sulphathiazole, that the small risk is amply justified by the tremendous reduction in such a serious cause of manpower loss.

D.F.

SURGERY

The Effect of Surgical Operations on Blood Pressure

By J. D. Adamson and Sara Dubo
C.M.A.J., Sept., 1943

Many forms of treatment for essential hypertension have been advocated. Curiously enough, in discussing the results of different forms of treatment, it is often claimed that one-third of patients show improvement, one-third are unchanged, and one-third become worse. Two facts influence the interpretation of therapeutic results. Not only may the wide normal variations of blood pressure, present in every individual, prove misleading, but also any treatment may readily influence subjective symptoms commonly ascribed to "blood pressure."

The significance of normal variations in blood pressure is borne out by this example. A healthy youth, spending a quiet day at home, was observed and, though the individual was subject to no physical or emotional strain, the systolic pressure varied from 105 to 135 and the diastolic from 65 to 90 in response to change of posture, digestion and sedentary work.

In essential hypertension normal stimuli produce responses that are abnormally profound or prolonged. For example, a patient, who was encouraged to relax and try to sleep, had a fall in pressure of from 170-100 to 135-85 in fifteen minutes. This non-therapeutic oscillation is worthy of note.

Symptoms provide a poor index for measuring therapeutic effects because hypertension produces no special subjective feelings till the late stages, when the heart, brain and kidney have become secondarily involved. Many patients develop symptoms mainly because of a fear of hypertension and these individuals prove very responsive to most forms of treatment.

A study was made during the hospitalization of 208 cases before and after various major operations, and 28 additional cases with hypertension who were not operated on. Both the operative and non-operative groups showed a definite and similar reduction in blood pressure. In those cases with hypertension, the fall in pressure was much greater, expressed either as mm. of Hg., or as a percentage drop. The reduction was comparable to that which has usually been attributed to specific operations on the sympathetic nervous system. Subjective symptoms tended to disappear during hospitalization whether or not an operation was performed.

The authors conclude that the fall in blood pressure associated with major surgery is chiefly due to the general effect of hospitalization and not to any specific effect of the operation. This fact should be kept in mind when assessing the results claimed for alleged specific surgical measures.

W. B. S.

Perforating Wounds of the Intestine: Satisfactory Method of Treatment for Wounds More than Twenty-four Hours Old

By Thomas B. Noble, Jr., M.D.
American Journal of Surgery, Oct., 1943

In the last war, perforating wounds of the intestine, treated after 24 hrs. following the injury, were attended by a mortaliy of 90%. Routine autopsy of such cases revealed well-established general peritonitis, with exudation, fluid accumulation, and multiple abscesses. Marked distension of the small bowel, with kinking, angulation, gangrene, and mesenteric thrombosis were unfailing autopsy findings. The author notes that a similar picture is found in civilian cases of gunshot and stab wounds, football injuries, auto accidents, ruptured appendices and cysts, pneumoccic peritonitis, ruptured ulcers, and many other conditions causing general peritonitis.

The general peritoneal inflammation soon passes off in most cases, to be replaced by multiple localized abscess formation. It is at the sites of localization that intestinal obstructions occur. The author feels that exudation, swelling, and distension of the bowel, as a result of such obstructions, are responsible for the non-union of the sutured perforations; and the gangrene of gut and mesentery at the abscess sites, together with the obstructions, are responsible for the fatal toxaemia. Thus, death is due to the effects of the mechanism of localization and recovery from peritonitis.

Treatment suggested by the author is based on the principles of removal of obstructions already present at the sites of local abscess formation, and the prevention of future obstructions at the sites of sutures, traumatized peritoneum, and damaged omentum.

The adherent obstructed loops of bowel are first dissected from their attachments. This involves cutting through abscess walls, thus leaving areas of gut without peritoneum. Such raw, oozing surfaces cannot be replaced in the abdominal cavity because they will form new adhesions. To prevent such adhesions, the technique of plication is employed. This consists of a method of sewing adjacent lengths of bowel together, in a manner described by the author, so as to form artificial regular loops containing the stripped surfaces and suture points within the loops, on the contiguous surfaces, so that adhesions with other loops of bowel are impossible. By this means, the obstructive irregular adhesions arising from the peritonitis are replaced by controlled regular loops

which do not affect the patency of the intestine. The entire procedure is clearly explained by nineteen photographs and diagrams.

A case is reported, of one patient, on whom the performance of a subsequent unrelated operation 14 months later, afforded an opportunity to examine the bowel thus treated. It was found to be perfectly normal, as clinical histories of previous patients had indicated.

The author stresses the importance of the use of sulphonamides, plasma, and spinal anaesthesia in improving the patient's chances of recovery. But the most important measure is *complete* treatment of every injured area of peritoneum in the manner described. A drain is always left, to remove pus collecting in the pelvis post-operatively. Further post-operative measures are outlined.

By this method of treatment, the chances of survival have been raised from 10% to 90%.

H.K.

OBSTETRICS AND GYNECOLOGY

Practical Aspects of Endocrine Therapy

By S. C. Freed
Western Journal of Surg., Obs., and Ggn., Oct., 1943

Much of the confusion that exists in endocrine therapy is due to over-enthusiasm and over-expectation, and the discouragements that have been met are due to use of the drugs where there was no sound basis. Where the indications are proper, one may get very good results. There are now many crystalline compounds and highly purified extracts on the market and simple extracts and dessicated glands are falling into disuse.

Anterior Pituitary extract has been, on the whole, rather disappointing since it is not sufficiently potent, and is as yet too expensive for any wide use. The gonadotropic hormone preparations have shown little or no effect on the ovary. The lactogenic preparations have some value in stimulating milk flow. Preparations containing many factors (called soup) have little value, since there is not enough gland used in the preparation of a unit volume, and many of them deteriorate on standing.

Gonadotropins are usually prepared from the urine of placenta of pregnant women, or from the serum of pregnant mares. These are standardized to an international standard. The chorionic type, from the urine and placenta of women, is of value in cryptorchidism where there is no anatomical barrier to the descent of the testis. In these cases it is necessary to differentiate between true cryptorchidism and the pseudocryptorchidism caused by reflex spasm. It is of doubtful value in uterine bleeding and long administration may cause changes in the ovary. The preparations from pregnant mares' serum has only questionable value in sterility, since only normal women who would ovulate anyway have been made to ovulate with it. Its use in ovarian dysfunction is difficult to evaluate.

Estrogens are now prepared in pure potent forms. The assay is difficult since as much as 1,000% difference has been found in the rat units in different labs. There have been several synthetic estrogens prepared in the last few years. The most widely used is diethylstilbestrol, or commonly known, stilbestrol. This is several times as potent as estrone, and is inexpensive to prepare as compared with the natural extracts. It is commonly administered orally. Doses of 0.5-1.0 mg. per day, orally, are given to relieve menopausal symptoms. The chief difficulty is

that in 10-20% there are unpleasant symptoms such as nausea, vomiting, headache, and dizziness. There has been no demonstration that these symptoms are due to tissue damage, but are possibly systematic reactions similar to those in early pregnancy. These symptoms decrease when the absorption into the blood is retarded. This retardation may be accomplished by using the fatty acid esters of the estrogenic substances.

Some estrogenic preparations are: hexestrol, an English preparation which Freed finds to be about 1/5 as effective therapeutically as stilbestrol, though less toxic. Octofollin is a synthetic preparation, effective without undue toxicity. Dinestrol has been introduced in England by Barnes and is claimed to be several times as potent as stilbestrol. Premarin is a natural estrogen prepared as the mixture of sulfate conjugated estrogens of pregnant mares' urine. It is given by mouth with good results in menopausal patients. Estrogenic therapy is of undoubted value in the menopause and menopausal complications such as senile vaginitis and kraurosis.

In ovarian dysfunctions there has been no uniform procedure followed as yet. In amenorrhea, estrogens may be administered to induce uterine bleeding. Large doses, 10-30 mgs. are required. Whether this is worth while or not depends on the desire of the patient. The therapy must be repeated in courses in order to produce cyclical bleeding, since most patients stop having menstrual cycles after the estrogens are withdrawn. Psychic reasons seem to be the only worthwhile uses. Some who have functional amenorrhea may continue to have cycles after the cessation of therapy. This type of response is termed "shaking the clock."

In the treatment of dysmenorrhea, estrogens have been given in the first two weeks of the cycles and the effect in relieving dysmenorrhea results from the complete or partial suppression of ovulation. Such treatment is merely temporary and requires repeated courses of therapy.

In the treatment of uterine bleeding, an injection of estrogen in oil into the cervix often brings almost immediate control of the bleeding. In the suppression of lactation, good results have been found by the use of 5-15 mg. estrogen daily for two or three days in the early post-partum period to prevent engorgement of the breasts and also it may help relieve distress in weaning.

The choice of estrogens is regulated by the patient's requirement. At the menopause where long continued effect is desired, injection of the fatty acid ester of the estrogens is used. Estradiol dipalmitate is the best of the present commercial preparations. Estrone crystals in water is the most effective of the injectables, and it eliminates sensitivity often found with the oils.

In prostatic carcinoma estrogen administration is comparable to orchidectomy by removing the androgenic stimulus to prostatic tissues. The course of response may be followed by the serum acid phosphatase which is high in malignancy and depressed by estrogens and castration.

Progesterone, the corpus luteum hormone, is now prepared by chemical synthesis. The therapeutic use has been disappointing. It is of little value in ovarian dysfunction though it is helpful in relieving premenstrual tension, and possibly has some value in habitual abortion. Pregneninolone is available for oral administration, though only 1/5 as effective as injected progesterone.

Testosterone propionate is the most efficient androgenic substance for therapeutic use. The preparations of testicular

tissue and urine extracts are practically worthless. It is valuable in eunuchoid or castrated men. However, rather large doses (50-100 mg./wk) must be used. The symptoms and signs return with cessation of therapy. It is only of psychic value in treating senility and psychic impotence. It is not used for disorders of sperm formation. In some ovarian dysfunctions, as dysmenorrhea, menorrhagia, painful breasts, and premenstrual tension it is used, though large doses, 100-500 mg./month are required. An oral preparation is available in the form of methyl testosterone, but four times as much is required by mouth as by injection. Ointments are of insufficient strength for other than suggestive value.

Adrenal cortex is valuable in Addison's Disease. It is quite doubtful if it is of any value in asthenia or toxaemias. Oral preparations require huge amounts, so are too expensive for most people. A synthetic preparation, desoxycorticosterone acetate is valuable in Addison's, but overdosage may result in hypertension or heart failure. It is being investigated at present to determine its value in treatment of shock.

K.M.J.

The Value of the Vaginal Smear in the Diagnosis of Uterine Cancer

By Joe Vincent Meigs, M.D., F.A.C.S., Ruth N. Graham, B.S., Maurice Fremont-Smith, M.D., F.A.C.P., Israel Kapnick, M.D., and Ruben W. Rawson, M.D.,
Boston, Massachusetts.

Surgery, Gynaecology, and Obstetrics, November, 1943

As the chances of curing carcinoma of the cervix are said to decrease between 3 and 4 per cent per week, it is of the utmost importance to diagnose this condition as early as possible. In the average case, the patient does not consult her doctor until about four months after the onset of bleeding; and another period of four months elapses before operation, because the physician hesitates to put the patient to the inconvenience of either examination, curettage, or biopsy. The result is that by the time the condition has been diagnosed, 60 per cent of the cases are inoperable, while only 11 per cent are still in the early stage.

Papanicolaou has diagnosed cervical and endometrial carcinoma by examining microscopically the vaginal secretion for the presence of tumour cells. The authors of the present article describe this method in detail and give the results that they have obtained on a series of 220 cases.

The material is collected by a glass pipette inserted up into the fornix of the vagina. It is essential, however, that the pipette be absolutely dry and that the vagina should not have been douched that day, as water changes the appearance of the cells to be studied. The material is squeezed out of the pipette onto a slide, fixed and put through a staining process which the ordinary physician could master with a little practice.

The authors describe in detail the cells which are present both in normal smears and in the smears of patients with uterine or vaginal carcinoma; and the article is illustrated with black and white photomicrographs and coloured reproductions of the cells. It is enough to say here that the cells are sufficiently characteristic that two of the authors examining independently smears from the 220 cases agreed upon the diagnosis in every case.

In this series of patients there were 62 cases of cancer. (*a*) In 45 out of 46 cases of cervical carcinoma positive smears were obtained (an error of 2.2%) and of these cases 10 were *early* carcinomata. (*b*) Eleven out of 12 cases of endometrial

carcinoma were diagnosed by this method (an error of 8.3%) and 5 of these were *early* cases. (*c*) Of the remaining 4 cases, 3 were carcinomata of the vagina and one was carcinoma of the rectum with a recto-vaginal fistula, all of which gave positive vaginal smears.

Out of 153 cases in which carcinoma was *not* present, positive smears were obtained in 4 cases—an error of 2.6%.

These results indicate that the vaginal smear cannot be relied upon in every case. Therefore, if a smear be negative, the test should be repeated a number of times before the results are accepted; while, on the other hand, if a positive result be obtained, the patient ought not to be subjected to operation until either curettage of a biopsy has been done.

K.F.C.

PAEDIATRICS

Aetiology of Erythroblastosis Foetalis and Certain Transfusion Reactions with Special Reference to the Rh Factor

By P. L. Mollison

Proc. Roy. Soc. Medicine, March, 1943

For some time it has been recognized that the clinical entities hydrops foetalis, icterus gravis neonatorum and congenital anaemia of the new-born (all included in the term erythroblastosis foetalis) are manifestations of the same disease process, an hemolysis of red blood cells. But not until 1940 was light shed on the aetiology of this hemolytic process.

In that year it was shown that there existed in the red blood cells of 85% of American whites an agglutinogen termed Rh because a similar antigen was present in the red cells of Rhesus monkeys. These individuals were classed as Rh positive. The remaining 15%, whose erythrocytes lacked the Rh agglutinogen (Rh-ve) were found to develop specific Rh agglutinins when transfused with Rh positive blood. Following this, anti-Rh agglutinins were discovered in the sera of women who were Rh -ve. The presence of these agglutinins was often associated with foetal morbidity, particularly with erythroblastosis foetalis. All the infants were Rh positive. These findings suggested that Rh agglutinogens passed from the foetus to the maternal blood across the placental membrane; the mother became sensitized and anti-Rh agglutinins were formed; these subsequently entered the foetal circulation and brought about hemolysis of the Rh positive red cells. In further support of this theory, it was demonstrated that Rh positive erythrocytes were rapidly destroyed in the circulation of these infants, whereas Rh -ve red cells survived for long periods—90 days or more. These observations are strong indication for the transfusion of these infants with Rh -ve blood only; and if there is any suspicion that a child has erythroblastosis and the mother requires a transfusion, only Rh -ve blood should be used for she has anti-Rh agglutinins in her blood stream.

Since in approximately 1 in 10 pregnancies the mother is Rh -ve and the infant Rh positive, other factors must come into play for otherwise erythroblastosis foetalis would be far more common. Two possible considerations are the failure of the Rh agglutinogen to cross the placenta in adequate amounts to stimulate the formation of anti-Rh agglutinins, and the failure of the mother to respond to the stimulation.

Transfusion reactions may occur in any Rh -ve individual who has received Rh positive blood. Though the response to the first transfusion may be satisfactory, subsequent transfusions bring increasing

danger as more and more anti-Rh agglutinins are formed.

Signs of a reaction are failure of the hemoglobin to rise after transfusion, development of jaundice, and hemoglobinuria.

J. C. L.

PHYSIOLOGY

The Use of the Eyes at Night

Liljencrantz, Swanson and Carson
United States Naval Institute Proceedings, June, 1942

This article, written primarily for naval personnel, discusses the means of improving vision at night through knowledge of the physiology of dark adaptation.

A. The Rods and Cones

These cells are the light sensitive endings of the optic nerve. They differ in 5 main respects.

1. *Distribution*

At the periphery of the retina there are only rods but as the centre is approached more and more cones appear until at the macula cones alone are present. Over the optic disc neither type of cell is found.

2. *Colour vision and sensitivity to light of varying wave length*

Only cones can distinguish colour but the sensitivity of both types of cell varies with the wave length of the light reaching the retina. The wave band in the region of 550 millimicrons (yellow) appears brightest to the cones while rods are most sensitive at 510 millimicrons, that is to light which appears blue green to the cones. Rods, however, are relatively insensitive to waves longer than 600 millimicrons and therefore do not function in the red region of the spectrum.

3. *Sensitivity to light of varying intensity*

Broadly speaking cone vision is day vision and rod vision night vision. The rod cells save us from complete night blindness for they are able to detect light down to 1/5000 of the intensity at which cone vision ceases. Cones do function, however, down to 1/1000 foot candle (about the level of bright moonlight). On the other hand rods function in bright light in addition to having very high sensitivity to dim light; and as there are no cones in the periphery of the retina, they are responsible for vision in the "corner" of the eye.

4. *Fine vision*

Rods do not permit vision in fine detail and this function is carried out by the cones.

B. Light and Dark Adaptation

Chemical changes in the rods bring about dark adaptation. This adjusting to darkness continues for more than an hour but the gain in sensitivity after 30 minutes is extremely slight. Then on exposure to bright light the eyes readily become light adapted after a brief period of dazzle. It is important to note this fact that the time required for light adaptation is very much less than that for dark adaptation, for 30 minutes spent in complete darkness in order to adjust to the dark may be entirely wasted by a brief exposure to bright light.

C. Methods for producing Dark Adaptation

The simplest means is to remain in complete darkness for at least a half an hour before going on a night mission. But a more useful stratagem is to make use of the fact that rods are insensitive to red light. This may be done in either of two ways. The first is to use sources of light which emit only light waves longer than 600 millimicrons. The second is to

employ ordinary incandescent illumination but provide personnel with red goggles which will shut out all light except the proper quality of red; this has the advantage that only those preparing for night observation duty need wear the red goggles while all others may carry on under normal illumination. Now red light permits vision with cones only; hence in order to see objects to one side or the other the eyes must be turned and fixed upon them, there being no cones at the periphery of the retina. In addition any red markings will not be visible when illuminated with red light or regarded through red goggles.

D. Rules for the Use of Dark Adapted Eyes

1. Avoid light. For instrument illumination use light for as brief periods as possible; better still employ red light.

2. The point of sharpest vision in the light-adapted eye is the visual centre or macula and we habitually fix our attention on objects in such a way that their images are thrown on this area. In dim illumination, however, this rod-free region is blind and the gaze must be directed slightly above, below or to the side in order that an image may fall on a portion of the retina in which rods are present.

3. Night vision is colourless vision and therefore wholly dependent on contrast. Anything which reduces contrast such as haze, fog, dirt or scratchings on windshields and goggles will seriously impair night vision. Such surfaces, then, should be kept scrupulously clean.

4. Remember that rods do not permit vision in fine detail and small objects cannot be seen at night.

5. Night vision is one of the first faculties to be affected adversely and insidiously by failure to use oxygen above 6 to 8000 feet. Instrument markings seem dimmer; the pilot turns on panel lights more and more brightly, thus starting a vicious circle. Use of oxygen in flying at night, therefore, should begin at lower altitudes than in the day time.

6. Health should be maintained at peak with a liberal well-balanced diet and the avoidance of fatigue. Heavy smoking and alcoholling impair visual efficiency.

J. C. L.

QUESTION: *How would canned infant and junior foods be of value in the feeding program of my baby?*

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American Can Company, Hamilton, Ontario;
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(1) 1938, Am. J. Diseases Children 55, 1158.
1939, Hygeia 17, 171.
1940, Calif. and Western Med. 53, 18.
1941, J. Am. Dietet. Assn. 17, 861.
1941, Arch. Pediatrics 58, 40.

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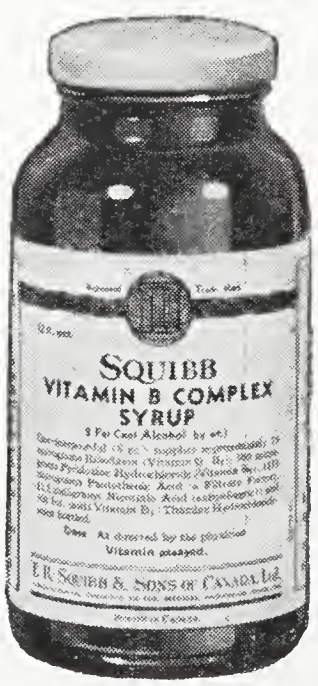

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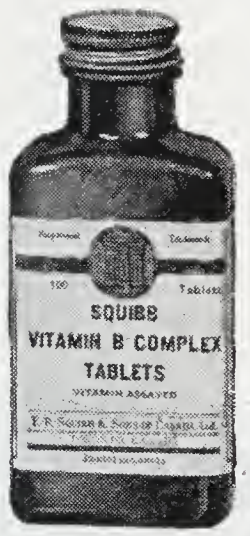

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